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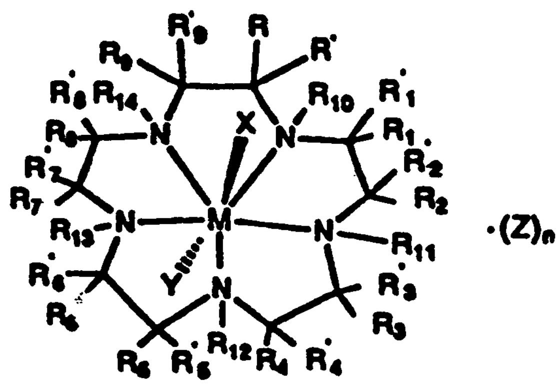

(I)

(57) Abstract

Th present invention is directed to complexes represented by formula (I) wherein R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, R'_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, M, X, Y, Z and N are defined herein for use as contrast agents in diagnostic imaging.

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DIAGNOSTIC IMAGE ANALYSIS WITH METAL COMPLEXES

Background of the Invention

This invention relates to compounds effective as contrast agents in diagnostic imaging. In one aspect, this invention relates to magnetic resonance imaging (MRI) of human or non-human animal subjects using metal complexes of substituted nitrogen-containing fifteen-membered macrocyclic ligands as contrast agents. In another aspect, this invention relates to manganese(II) complexes of substituted nitrogen-containing fifteen-membered macrocyclic ligands as MRI contrast agents.

X-rays have long been used to produce images of human and non-human animal tissue, e.g. the internal organs of a patient, the patient being positioned between a source of X-rays and a film sensitive to the rays. Where organs interfere with the passage of the rays, the film is less exposed and the resulting developed film is indicative of the state of the organ.

More recently, nuclear magnetic resonance (NMR) has been developed as an imaging technique, i.e. MRI. MRI avoids the harmful effects sometimes attending X-ray exposure. For improved imaging with X-rays, patients have been given enhancers prior to imaging, either orally or (parenterally). After a predetermined time interval for distribution of the enhancer through the patient, the image is taken. To obtain a good image it is desirable that the time after the taking of enhancer be kept to a minimum. On the other hand there is a decrease in effectiveness with time, so desirably the decay should be relatively slow so as to provide a substantial time interval during which imaging can be done.

substantial time interval during which imaging can be done.

In the NMR imaging process, protons in the water of the body relax via two mechanisms referred to as T_1 and T_2. The rate at which the relaxation process occurs may be altered for some water molecules by giving values that contrast with the norm.

Compounds that enhance NMR images, referred to as contrast agents, are generally paramagnetic in nature. These may be organic free radicals or transition/lanthanide metals which have from one to seven unpaired electrons.

A necessary prerequisite of any ligand that binds a metal to form a contrast agent is that the resulting contrast agent be stable so as to prevent the loss of the metal and its subsequent accumulation in the body. Other considerations include an ability to reversibly bind water, which in turn increases it contrastability and decreases the dose level required. This ability is clearly important since the interaction between any two nuclear spins through space decreases at a rate equal to the reciprocal of the distance raised to the sixth power.

U.S. Pat. No. 4,647,447 discloses use of an NMR image enhancer consisting of the salt of an anion of a complexing acid and a paramagnetic metal anion. A preferred embodiment is the gadolinium chelate of diethylenetriaminepentaacetic acid (Gd DTPA), which is now commercially available from Nycomed Salutar, Inc. under the trade name Magnevist for use as an NMR contrast agent. From the data reported therein these appear to perform well. However, this compound is rapidly excreted by th kidneys, making the timing of the inj cti n extremely critical. Furthermor , ther is virtually no uptake by any solid organ, such as the h art, pancreas or liver.

However, while a number of gadolinium contrast agents are known, there remains the possibility that small amounts of free lanthanides are being released, by decomposition of the agent, into the body. Not being a naturally existing metal in the body, little is known about long term effects.

Other nitrogen-containing macrocyclic ligands have been suggested for use as NMR contrast agents. Jackels, S. C. et al, "Aqueous Proton NMR Relaxation Enhancements by Manganese(II) Macrocyclic Complexes: Structure-Relaxivity Relationships", *Inorg. Chem.*, 31, 234-239 (1992) discloses fifteen-membered nitrogen-containing ring complexes. However, these compounds suffer from being insufficiently stable and/or colored, and as such are inadequate for application as MRI contrast agents.

Therefore, it would be highly desirable to develop alternative contrast agents which avoid one or more of the aforementioned disadvantages.

It has now been discovered that metal complexes of substituted nitrogen-containing macrocyclic ligands which have increased kinetic, thermodynamic and oxidative stability, and which can be substituted to control lipophilicity, i.e. biodistribution, avoid the problems of the aforementioned contrast agents while providing good contrastability.

SUMMARY OF THE INVENTION

It is an object of the invention to provide magnetic resonance imaging (MRI) contrast agents having improved kinetic stability, i.e. the rate at which the paramagnetic metal dissociates from the metal complexes of th inv ntion. It is a further object of the invention to provide MRI c ntrast agents in which the biodistribution of the contrast agents can be

controlled. It is yet a further object of the invention to provide MRI contrast agents having improved oxidative stability and improved hydrogen bonding. It is a still further object of the invention to provide metal complexes which are useful as X-ray or ultrasound contrast agents, and which can be used in scintigraphy and radiotherapy.

According to the invention, a method of magnetic resonance imaging is provided which comprises administering to a human or non-human animal subject a contrast medium comprising a physiologically compatible paramagnetic metal complex of the present invention and a non-toxic, pharmaceutically acceptable carrier, adjuvant or vehicle, and generating a magnetic residence image of at least a part of the subject.

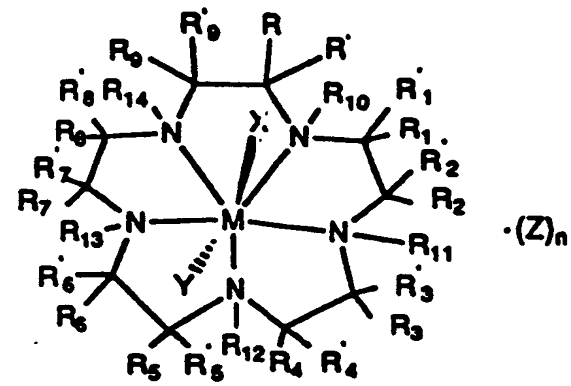
Further according to the invention, a method of diagnostic imaging is provided which comprises administering to a human or non-human animal subject a diagnostic agent comprising a physiologically compatible heavy metal complex of the present invention and a non-toxic, pharmaceutically acceptable carrier, adjuvant or vehicle, and generating an X-ray, ultrasound or scintigraphic image of at least a part of the subject.

Further according to the invention, a method of radiotherapy practiced on a human or non-human animal subject is provided which comprises administering to the subject a radioactive agent comprising a physiologically compatible radioactive metal complex of the present invention and a non-toxic, pharmaceutically acceptable carrier, adjuvant or vehicle.

DETAILED DESCRIPTION OF THE INVENTION

Th m tal complexes of th invention used as MRI contrast agents, as diagnostic agents in X-ray, ultra-

sound or scintigraphic image analysis, or as radiotherapy agents are represented by the formula:



wherein R, R′, R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, and R'_9 independently are selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylcycloalkyl, cycloalkenylalkyl, alkylcycloalkyl, alkenylcycloalkyl, alkylcycloalkenyl, alkenylcycloalkenyl, heterocyclic, aryl and aralkyl radicals and radicals attached to the α-carbon of α-amino acids; or R_1 or R'_1 and R_2 or R'_2, R_3 or R'_3 and R_4 or R'_4, R_5 or R'_5 and R_6 or R'_6, R_7 or R'_7 and R_8 or R'_8, and R_9 or R'_9 and R or R′ together with the carbon atoms to which they are attached independently form a saturated, partially saturated or unsaturated cyclic having 3 to 20 carbon atoms; R and R′, R_1 and R'_1, R_2 and R'_2, R_3 and R'_3, R_4 and R'_4, R_5 and R'_5, R_6 and R'_6, R_7 and R'_7, R_8 and R'_8, and R_9 and R'_9 together with the carbon atoms to which they are attached independently form a saturated, partially saturated, or unsaturated ring structure having 3 to 20 carbon atoms; or one of R, R′, R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, R'_9, R_{10},

R_{11}, R_{12}, R_{13} and R_{14} together with a different one of R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, R'_9, R_{10}, R_{11}, R_{12}, R_{13} and R_{14} which is attached to a different carbon or nitrogen atom in the macrocyclic ligand may be bound to form a strap represented by the formula

$$-\!(CH_2)_x-M-\!(CH_2)_w-L-\!(CH_2)_z-J-\!(CH_2)_y-$$

wherein w, x, y and z independently are integers from 0 to 10, and M, L and J are independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, alkaryl, alkheteroaryl, aza, amide, ammonium, thia, sulfonyl, sulfinyl, sulfonamide, phosphonyl, phosphinyl, phosphino, phosphonium, keto, ester, carbamate, urea, thiocarbonyl, borates, boranes, boraza, silyl, siloxy, silaza and combinations thereof; and R_{10}, R_{11}, R_{12}, R_{13} and R_{14} independently are selected from the group consisting of hydrogen, alkyl, and alkyl substituted with $-OR_{15}$, $-COOR_{15}$, $-CONR_{15}R_{16}$ or $-PO_3H_2$ wherein R_{15} and R_{16} are independently hydrogen or alkyl; and wherein at least two of R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9 and R'_9 are other than hydrogen.

X, Y and Z represent suitable ligands or charge-neutralizing anions which are derived from any monodentate or polydentate coordinating ligand or ligand system or the corresponding anion thereof (for example benzoic acid or benzoate anion, phenol or phenoxide anion, alcohol or alkoxide anion). X, Y and Z are independently selected from the group consisting of halide, oxo, aquo, hydroxo, alcohol, phenol, dioxygen, peroxo, hydroperoxo, alkylperoxo, arylperoxo, ammonia, alkylamino, arylamino, heterocycloalkyl amino, heterocycloaryl amino, amine xides, hydrazin , alkyl hydrazin , aryl hydrazin , nitric oxide, cyanide, cyanate, thiocyanate, isocyanate, isothiocyanate, alkyl nitrile, aryl nitrile, alkyl isonitril , aryl

isonitrile, nitrate, nitrite, azido, alkyl sulfonic acid, aryl sulfonic acid, alkyl sulfoxide, aryl sulfoxide, alkyl aryl sulfoxide, alkyl sulfenic acid, aryl sulfenic acid, alkyl sulfinic acid, aryl sulfinic acid, alkyl thiol carboxylic acid, aryl thiol carboxylic acid, alkyl thiol thiocarboxylic acid, aryl thiol thiocarboxylic acid, alkyl carboxylic acid (such as acetic acid, trifluoroacetic acid, oxalic acid), aryl carboxylic acid (such as benzoic acid, phthalic acid), urea, alkyl urea, aryl urea, alkyl aryl urea, thiourea, alkyl thiourea, aryl thiourea,alkyl aryl thiourea, sulfate, sulfite, bisulfate, bisulfite, thiosulfate, thiosulfite, hydrosulfite, alkyl phosphine, aryl phosphine, alkyl phosphine oxide, aryl phosphine oxide, alkyl aryl phosphine oxide, alkyl phosphine sulfide, aryl phosphine sulfide, alkyl aryl phosphine sulfide, alkyl phosphonic acid, aryl phosphonic acid, alkyl phosphinic acid, aryl phosphinic acid, alkyl phosphinous acid, aryl phosphinous acid, phosphate, thiophosphate, phosphite, pyrophosphite, triphosphate, hydrogen phosphate, dihydrogen phosphate, alkyl guanidino, aryl guanidino, alkyl aryl guanidino, alkyl carbamate, aryl carbamate, alkyl aryl carbamate, alkyl thiocarbamate aryl thiocarbamate, alkyl aryl thiocarbamate, alkyl dithiocarbamate, aryl dithiocarbamate, alkyl aryl dithiocarbamate, bicarbonate, carbonate, perchlorate, chlorate, chlorite, hypochlorite, perbromate, bromate, bromite, hypobromite, tetrahalomanganate, tetrafluoroborate, hexafluorophosphate, hexafluoroantimonate, hypophosphite, iodate, periodate, metaborate, tetraaryl borate, tetra alkyl borate, tartrate, salicylate, succinate, citrate, ascorbate, saccharinate, amino acid, hydroxamic acid, thiotosylat , and anions of ion exchange resins, or systems wh re one r m re of X,Y and Z are independently attached to one or more of the "R" groups, wherein n is

an integer from 0 to 3. The preferred ligands from which X, Y and Z are selected include halide, organic acid, nitrate and bicarbonate anions.

The metal atoms or anions, M, which are suitable for use in the complexes of the invention as MRI contrast agents are paramagnetic metals having atomic numbers 21-29, 42-44 and 57-71. The complexes for use as MRI contrast agents are those wherein the preferred metal is Eu, Gd, Dy, Ho, Cr, Mn or Fe, more preferably Gd(III) or Mn(II), and most preferably Mn(II).

The metal atoms or anions, M, which are suitable for use in the complexes of the invention as X-ray or ultrasound contrast agents are heavy metals having atomic numbers 20-32, 42-44, 49 and 57-83. The complexes for use as X-ray or ultrasound contrast agents are those wherein the preferred metal is a non-radioactive metal having atomic numbers 42-44, 49 and 57-83, and most preferably Gd, Dy or Yb.

The metal atoms or anions, M, of the complexes of the invention which are suitable for use in scintigraphic and radiotherapy are radioactive metals of any conventional complexable radioactive metal isotope, preferably those having atomic numbers 20-32, 42-44, 49 and 57-83. In scintigraphy, the most preferred metals are ^{99m}Tc or ^{111}In. In radiotherapy, the most preferred metals are ^{153}Sm, ^{67}Cu or ^{90}Y.

As utilized herein, the term "alkyl", alone or in combination, means a straight-chain or branched-chain alkyl radical containing from 1 to about 22 carbon atoms, preferably from about 1 to about 18 carbon atoms, and most preferably from about 1 to about 12 carbon atoms. Examples of such radicals include, but are not limited to, methyl, thyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, is -amyl, hexyl, octyl, nonyl, decyl, dodecyl, tetrad cyl, hexadecyl, octadecyl and eicosyl. The term "alkenyl",

alone or in combination, means an alkyl radical having one or more double bonds. Examples of such alkenyl radicals include, but are not limited to, ethenyl, propenyl, 1-butenyl, cis-2-butenyl, trans-2-butenyl, iso-butylenyl, cis-2-pentenyl, trans-2-pentenyl, 3-methyl-1-butenyl, 2,3-dimethyl-2-butenyl, 1-pentenyl, 1-hexenyl, 1-octenyl, decenyl, dodecenyl, tetradecenyl, hexadecenyl, cis- and trans- 9-octadecenyl, 1,3-pentadienyl, 2,4-pentadienyl, 2,3-pentadienyl, 1,3-hexadienyl, 2,4-hexadienyl, 5,8,11,14-eicosatetraenyl, and 9,12,15-octadecatrienyl. The term "alkynyl", alone or in combination, means an alkyl radical having one or more triple bonds. Examples of such alkynyl groups include, but are not limited to, ethynyl, propynyl (propargyl), 1-butynyl, 1-octynyl, 9-octadecynyl, 1,3-pentadiynyl, 2,4-pentadiynyl, 1,3-hexadiynyl, and 2,4-hexadiynyl. The term "cycloalkyl", alone or in combination means a cycloalkyl radical containing from 3 to about 10, preferably from 3 to about 8, and most preferably from 3 to about 6, carbon atoms. Examples of such cycloalkyl radicals include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and perhydronaphthyl. The term "cycloalkylalkyl" means an alkyl radical as defined above which is substituted by a cycloalkyl radical as defined above. Examples of cycloalkylalkyl radicals include, but are not limited to, cyclohexylmethyl, cyclopentylmethyl, (4-isopropylcyclohexyl)methyl, (4-t-butyl-cyclohexyl)methyl, 3-cyclohexylpropyl, 2-cyclohexylmethylpentyl, 3-cyclopentylmethylhexyl, 1-(4-neopentylcyclohexyl)methylhexyl, and 1-(4-isopropylcyclohexyl)methylheptyl. The term "cycloalkylcycloalkyl" means a cycloalkyl radical as defined ab v which is substituted by another cycloalkyl radical as defined above. Examples of cycloalkylcycloalkyl radicals include, but are not

limited to, cyclohexylcyclopentyl and cyclohexylcyclohexyl. The term "cycloalkenyl", alone or in combination, means a cycloalkyl radical having one or more double bonds. Examples of cycloalkenyl radicals include, but are not limited to, cyclopentenyl, cyclohexenyl, cyclooctenyl, cyclopentadienyl, cyclohexadienyl and cyclooctadienyl. The term "cycloalkenylalkyl" means an alkyl radical as defined above which is substituted by a cycloalkenyl radical as defined above. Examples of cycloalkenylalkyl radicals include, but are not limited to, 2-cyclohexen-1-ylmethyl, 1-cyclopenten-1-ylmethyl, 2-(1-cyclohexen-1-yl)ethyl, 3-(1-cyclopenten-1-yl)propyl, 1-(1-cyclohexen-1-ylmethyl)pentyl, 1-(1-cyclopenten-1-yl)hexyl, 6-(1-cyclohexen-1-yl)hexyl, 1-(1-cyclopenten-1-yl)nonyl and 1-(1-cyclohexen-1-yl)nonyl. The terms "alkylcycloalkyl" and "alkenylcycloalkyl" mean a cycloalkyl radical as defined above which is substituted by an alkyl or alkenyl radical as defined above. Examples of alkylcycloalkyl and alkenylcycloalkyl radicals include, but are not limited to, 2-ethylcyclobutyl, 1-methylcyclopentyl, 1-hexylcyclopentyl, 1-methylcyclohexyl, 1-(9-octadecenyl)cyclopentyl and 1-(9-octadecenyl)cyclohexyl. The terms "alkylcycloalkenyl" and "alkenylcycloalkenyl" means a cycloalkenyl radical as defined above which is substituted by an alkyl or alkenyl radical as defined above. Examples of alkylcycloalkenyl and alkenylcycloalkenyl radicals include, but are not limited to, 1-methyl-2-cyclopentyl, 1-hexyl-2-cyclopentenyl, 1-ethyl-2-cyclohexenyl, 1-butyl-2-cyclohexenyl, 1-(9-octadecenyl)-2-cyclohexenyl and 1-(2-pentenyl)-2-cyclohexenyl. The term "aryl", alone or in c mbination, means a phenyl r naphthyl radical which pti nally carries on or more substituents selected from alkyl, cycloalkyl, cycloalkenyl, phenyl, naphthyl, h terocycl , alkoxyaryl,

alkaryl, alkoxy, halogen, hydroxy, amine, cyano, nitro, alkylthio, phenoxy, ether, trifluoromethyl and the like, such as phenyl, p-tolyl, 4-methoxyphenyl, 4-(tert-butoxy)phenyl, 4-fluorophenyl, 4-chlorophenyl, 4-hydroxyphenyl, 1-naphthyl, 2-naphthyl, and the like. The term "aralkyl", alone or in combination, means an alkyl or cycloalkyl radical as defined above in which one hydrogen atom is replaced by an aryl radical as defined above, such as benzyl, 2-phenylethyl, and the like. The term "heterocyclic" means ring structures containing at least one other kind of atom, in addition to carbon, in the ring. The most common of the other kinds of atoms include nitrogen, oxygen and sulfur. Examples of heterocyclics include, but are not limited to, pyrrolidinyl, piperidyl, imidazolidinyl, tetrahydrofuryl, tetrahydrothienyl, furyl, thienyl, pyridyl, quinolyl, isoquinolyl, pyridazinyl, pyrazinyl, indolyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, pyridinyl, benzoxadiazolyl, benzothiadiazolyl, triazolyl and tetrazolyl groups. The term "saturated, partially saturated or unsaturated cyclic" means fused ring structures in which 2 carbons of the ring are also part of the fifteen-membered macrocyclic ligand. The ring structure can contain 3 to 20 carbon atoms, preferably 5 to 8 carbon atoms, and can also contain one or more other kinds of atoms in addition to carbon. The most common of the other kinds of atoms include nitrogen, oxygen and sulfur. The ring structure can also contain more than one ring. The term "saturated, partially saturated or unsaturated ring structure" means a ring structure in which one carbon of the ring is also part of the fifteen-membered macrocyclic ligand. The ring structur can contain 3 to 20, pref rably 5 to 8, carbon atoms and can also contain nitrogen, oxygen and/or sulfur atoms. The term "organic acid ani n" refers to carboxylic acid anions having from about 1 to about 18

carbon atoms. The term "halide" means chloride or bromide.

The overall charge-type of the complex can be varied from negative to positive by nitrogen or carbon substitution of the appropriate charged groups on the macrocyclic framework. While the manganese (II) complexes of the invention exist as monocations in methanol solution, the axial anions are labile and in vivo can rapidly exchange with endogenous charged or uncharged ligands. By considering the dispositive nature of the manganese (II) metal center, the overall charge on the complex can be adjusted as needed to enhance desired pharmaceutical properties such as osmolality, tissue distribution and non-target clearance. For example, if the complex carries only charge neutral functionality, such as N- or C-alkyl substitution, then the overall charge on the complex will be determined by the manganese center and will be positive. Multi-positive complexes are available via the incorporation of pendant cations such as protonated aminoalkyl groups. These types of complexes can bind to endogenous anions, anionic proteins, cell membranes, and the like. If two pendant anionic groups are attached, such as two carboxylates, phenolate, phosphonates, sulfonates and the like, the overall charge on the complex can be envisioned as zero. Alternatively, if three or more pendant anionic groups are attached, the an anionic complex will result. The pendant groups may be designed to axially chelate and formally displace the axial anions or they may be designed specifically to not chelate but retain a charge type.

The substitutents on the complex of the invention, i.e. the "R" groups other than hydrogen, are those groups which result in complexes having improved stability, controlled lipophilicity, improved hydrogen bonding and greater rigidity of the macrocyclic ligand.

Regarding rigidity of the macrocycle, groups which rigidify the macrocycle result in improved stability and improved inner- and outer-sphere relaxation. Examples of groups which improve rigidity of the macrocycle include, but are not limited to, cycloalkyl groups e.g. trans-cyclohexano, and multiple alkyl groups, e.g. pentamethyl.

Regarding hydrogen bonding, groups that improve hydrogen bonding result in improved residence time of water to the metal complex by providing alternate binding sites. Examples of groups that improve hydrogen bonding include, but are not limited to, hydroxy alkyl, e.g. hydroxymethyl.

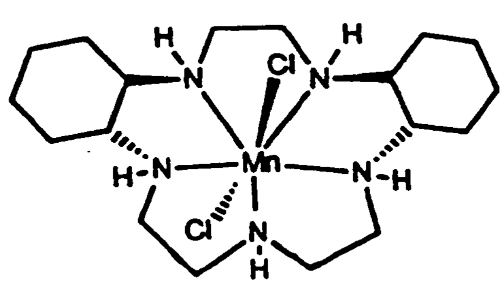
By varying the type and number of substitutents, e.g. "R" groups which are other than hydrogen, the lipophilicity of the complexes can be controlled, i.e. the biodistribution of the complexes of the invention can be controlled, by preparing compounds which vary from hydrophilic to lipophilic. Therefore, the complexes of the invention can be targeted to various tissues or organs in the body by controlling the type and number of substitutents.

Kinetic stability of the metal complex is important because complexes which are not sufficiently kinetically stable dissociate and release free metal in the body. The kinetic stability, k_{diss} ($M^{-1}sec^{-1}$), can be controlled by varying the type and number of substitutents which are other than hydrogen. The complexes of the invention have $k_{diss} \leq$ to 1400 $M^{-1}sec^{-1}$, i.e. the complexes of the invention are at least twice as stable as the complex in which all R's are hydrogen. In addition, the type and number of substitutents can be selected to give complexes which are at least 1000 times more kin tically stabl than the complex in which all R's are hydrogen. Examples of groups that improve kinetic stability include, but are not limited to, cycloalkyl groups, e.g.

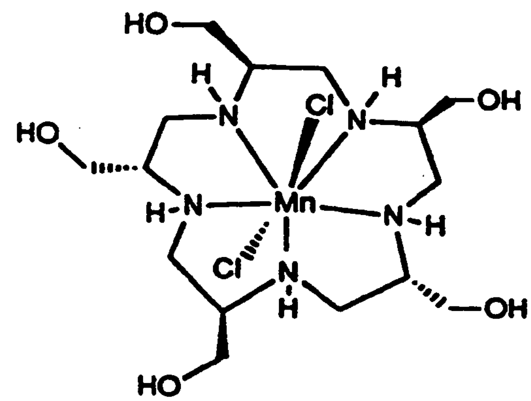
trans-cyclohexano, and multiple alkyl groups, e.g. penta- methyl. Oxidative stability of the metal complex is a particular problem for Mn complexes and is important because complexes which are not sufficiently oxidatively stable will go from Mn(II) to Mn(III). Since the Mn(III) complexes are colored, it is necessary to maintain the complexes in the Mn(II) form to have an effective contrast agent. By varying the type and number of substitutents, the oxidative stability, $E_{1/2}$(v), is controlled. It is generally desired to select the type of number of substitutents such that $E_{1/2}$ is greater than about 0.7v.

The number of "R" groups attached to carbon atoms, i.e. R-R_9 and R'-R_9', which are other than hydrogen is preferably at least 3, and more preferably at least 5.

One group of currently preferred compounds are those in which at least one of R_1 or R'_1 and R_2 or R'_2, R_3 or R'_3 and R_4 or R'_4, R_5 or R'_5 and R_6 or R'_6, R_7 or R'_7 and R_8 or R'_8, and R_9 or R'_9 and R or R' together with the carbon atoms to which they are attached form a saturated cyclic having 5 to 8 carbon atoms; and all of the remaining "R" groups are independently selected from hydrogen, alkyl, or alkyl substituted with $-OR_{15}$ or $-NR_{15}R_{16}$ wherein R_{15} and R_{16} are independently hydrogen or alkyl. The number of saturated cyclic rings can vary from one to 5, but is preferably at least 2, and the most preferred saturated cyclic has a ring size of 6 carbon atoms, i.e. is a cyclohexano group. An example of such a compound is represented by the formula:



Another group of currently preferred compounds are those in which at least two of R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9 and R'_9 are alkyl or alkyl substituted with $-OR_{15}$ or $-NR_{15}R_{16}$ wherein R_{15} and R_{16} are independently hydrogen or alkyl. The number of "R" groups which are alkyl or substituted alkyl is preferably at least 3, and more preferably at least 5. An example of such a compound is represented by the formula:



A first embodiment of the invention relates to the above metal complexes wherein at least one of R_{10}, R_{11}, R_{12}, R_{13} and R_{14} is other than hydrogen.

A second embodiment of the invention relates to a method of magnetic resonance imaging comprising (a) administering to a human or non-human animal subject a contrast medium comprising a physiologically compatible complex of the invention and a nontoxic pharmaceutically acceptable carrier, adjuvant or vehicle; and (b) generating a magnetic resonance image of at least a part of the human or non-human animal subject.

A third embodiment of the invention relates to a method of diagnostic imaging comprising (a) administering t a human or non-human animal subject a diagnostic agent comprising a physiologically compatibl complex of th present invention and a nont xic, pharmaceutically acceptable carrier, adjuvant or

vehicle, and (b) generating an X-ray, ultrasound or scintigraphic image of at least a part of the human or non-human animal subject.

A fourth embodiment of the invention relates to a method of radiotherapy practiced on a human or non-human animal subject comprising administering to the human or non-human animal subject a radioactive agent comprising a physiologically compatible complex of the present invention wherein M is a radioactive metal, and a nontoxic, pharmaceutically acceptable carrier, adjuvant or vehicle.

The macrocyclic ligand used herein as a comparison to the complexes of the present invention wherein all R's are H can be prepared according to the general synthetic scheme A set forth below utilizing methods known in the art for preparation of certain intermediates and certain ligands. See, for example, Richman et al., *J. Am. Chem. Soc.*, 96, 2268 (1974); Atkins et al. *Org. Synth.*, 58, 86 (1978); and EP 287 465. Thus a triazaalkane is tosylated in a suitable solvent system to produce the corresponding tris(N-tosyl) derivative. Such derivative is then treated with a suitable base to produce the corresponding disulfonamide anion. The disulfonamide anion is then reacted with a di-O-tosylated di-N-tosylated diazaalkane diol to produce the corresponding pentatosylpentaazacycloalkane. The tosyl groups are then removed and the resulting compound is reacted with a manganese(II) compound under essentially anhydrous and anaerobic conditions to form the corresponding manganese(II) pentaazacycloalkane complex.

The macrocyclic ligands useful in the complexes of the present invention, wherein R_1, R'_1, R_3, R'_3, R_5, R'_5, R_7, R'_7, R_9 and R'_9 can b H or any functionality as pr viously described, can be prepar d acc rding to th general peptid method shown in Schem B s t forth

below. The procedure for preparing the cyclic peptide precursors from the corresponding linear peptides are the same or significant modifications of methods known in the art. See, for example, Veber, D.F. et al., J. Org. Chem., 44, 3101 (1979). The general method outlined in Scheme B below is an example utilizing the sequential solution-phase preparation of the functionalized linear pentapeptide from N-terminus to C-terminus. Alternatively, the reaction sequence to prepare the linear pentapeptide can be carried out by solid-phase preparation utilizing methods known in the art. The reaction sequence could be conducted from C-terminus to N-terminus and by convergent approaches such as the coupling of di- and tri-peptides as needed. Thus a Boc-protected amino acid is coupled with an amino acid ester using standard peptide coupling reagents. The new Boc-dipeptide ester is then saponified to the free acid which is coupled again to another amino acid ester. The resulting Boc-tri-peptide ester is again saponified and this method is continued until the Boc-protected pentapeptide free acid has been prepared. The Boc protecting group is removed under standard conditions and the resulting pentapeptide or salt thereof is converted to the cyclic pentapeptide. The cyclic pentapeptide is then reduced to the pentaazacyclopentadecane with lithium aluminum hydride or borane. The final ligand is then reacted with a manganese(II) compound under essentially anaerobic conditions to form the corresponding manganese(II) pentaazacyclopentadecane complex.

Scheme B was utilized for the synthesis of the complexes of Examples 3 and 5.

The R groups in the macrocycles produc d by the cyclic p ptid route, i.e., R_1, R'_1, R_3, R'_3, R_5, R'_5, R_7, R'_7, R_9 and R'_9, could be derived from the D or L forms of the amino acids Alanine, Aspartic acid,

Arginine, Asparagine, Cysteine, Glycine, Glutamic acid, Glutamine, Histidine, Isoleucine, Leucine, Lysine, Methionine, Proline, Phenylalanine, Serine, Tryptophan, Threonine, Tyrosine, Valine and /or the R groups of unnatural α-amino acids such as alkyl, ethyl, butyl, tert-butyl, cycloalkyl, phenyl, alkenyl, allyl, alkynyl, aryl, heteroaryl, polycycloalkyl, polycycloaryl, polycycloheteroaryl, imines, aminoalkyl, hydroxyalkyl, hydroxyl, phenol, amine oxides, thioalkyl, carboalkoxyalkyl, carboxylic acids and their derivatives, keto, ether, aldehyde, amine, nitrile, halo, thiol, sulfoxide, sulfone, sulfonic acid, sulfide, disulfide, phosphonic acid, phosphinic acid, phosphine oxides, sulfonamides, amides, amino acids, peptides, proteins, carbohydrates, nucleic acids, fatty acids, lipids, nitro, hydroxylamines, hydroxamic acids, thiocarbonyls, borates, boranes, boraza, silyl, siloxy, silaza, and combinations thereof.

The macrocyclic ligands useful in the complexes of the present invention can also be prepared by the diacid dichloride route shown in Scheme C set forth below. Thus, a triazaalkane is tosylated in a suitable solvent system to produce the corresponding tris(N-tosyl) derivative. Such a derivative is treated with a suitable base to produce the corresponding disulfonamide anion. The disulfonamide anion is dialkylated with a suitable electrophile to produce a derivative of a dicarboxylic acid. This derivative of a dicarboxylic acid is treated to produce the dicarboxylic acid, which is then treated with a suitable reagent to form the diacid dichloride. The desired vicinal diamine is obtained in any of several ways. One way which is useful is th preparation from an aldehyd by reaction with cyanide in the presence f ammonium chl ride foll wed by treatment with acid to produce the alpha ammonium nitrile. Th latter compound is reduced in the

presence of acid and then treated with a suitable base to produce the vicinal diamine. Condensation of the diacid dichloride with the vicinal diamine in the presence of a suitable base forms the tris(tosyl)diamide macrocycle. The tosyl groups are removed and the amides are reduced and the resulting compound is reacted with a manganese (II) compound under essentially anhydrous and anaerobic conditions to form the corresponding substituted pentaazacycloalkane manganese (II) complex.

Scheme C was utilized for the synthesis of the complexes of Example 2.

The vicinal diamines have been prepared by the route shown (known as the Strecker synthesis) and vicinal diamines were purchased when commercially available. Any method of vicinal diamine preparation could be used.

The macrocyclic ligands useful in the complexes of the present invention can also be prepared by the bis(haloacetamide) route shown in Scheme D set forth below. Thus a triazaalkane is tosylated in a suitable solvent system to produce the corresponding tris(N-tosyl) derivative. Such a derivative is treated with a suitable base to produce the corresponding disulfonamide anion. A bis(haloacetamide), e.g., a bis(chloroacetamide), of a vicinal diamine is prepared by reaction of the diamine with an excess of haloacetyl halide, e.g., chloroacetyl chloride, in the presence of a base. The disulfonamide anion of the tris(N-tosyl) triazaalkane is then reacted with the bis(chloroacetamide) of the diamine to produce the substituted tris(N-tosyl)diamide macrocycle. The tosyl groups are removed and the amides are reduced and the resulting compound is reacted with a manganese (II) compound under ssentially anhydrous and anaerobic conditions to form the corresponding substituted pentaazacycloalkane manganese (II) complex.

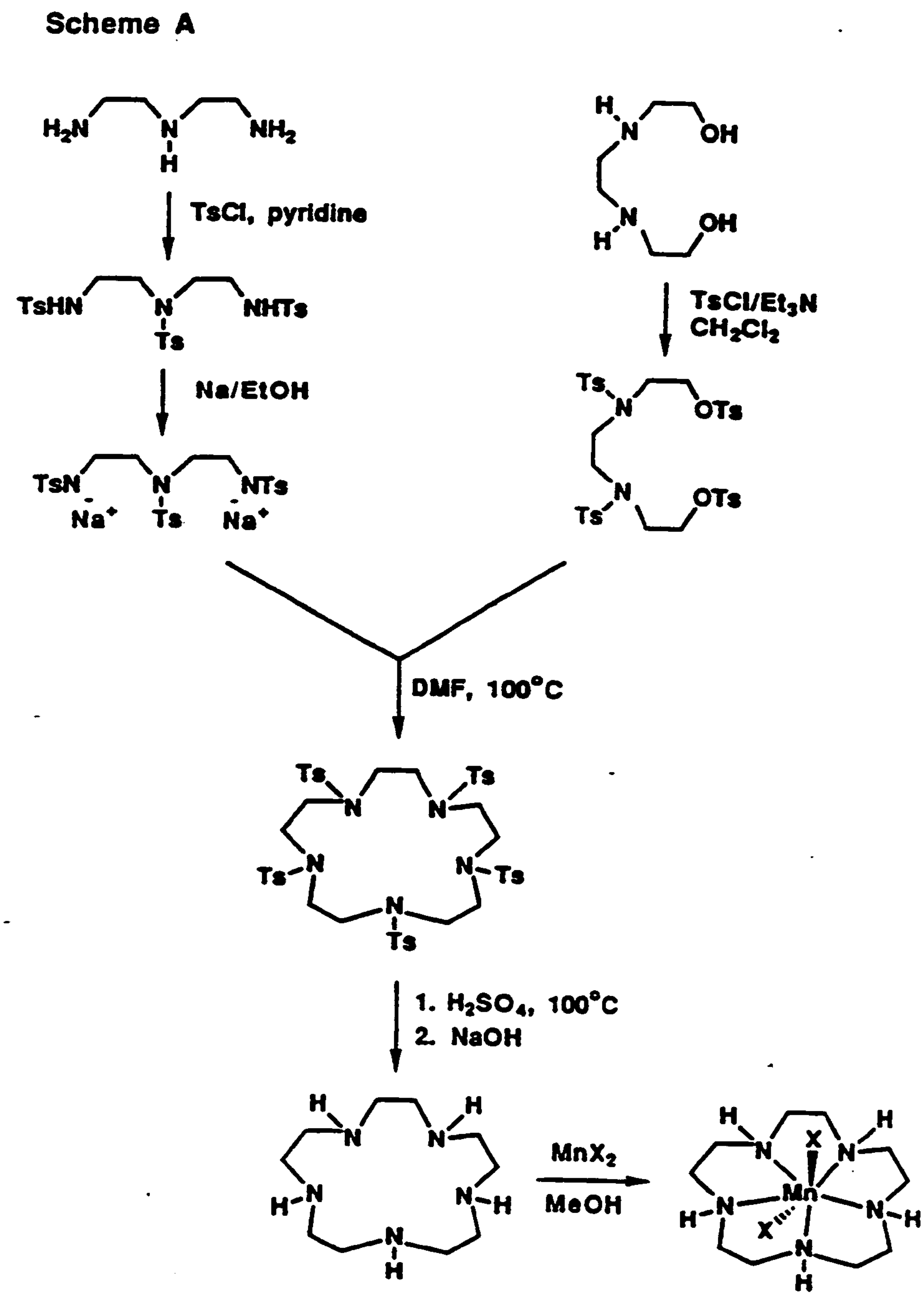
Scheme D is an alternative synthetic route to the complex of Example 2.

The macrocyclic ligands useful in the complexes of the present invention, wherein R_1, R'_1, R_2, R'_2 are part of a *cis*- or *trans*- cycloalkyl ring system and R_5, R'_5, R_7, R'_7 and R_9, R'_9 can be H or any functionality previously described, can be prepared according to the pseudo-peptide method shown in Scheme E set forth below. A *cis*-1,2-Diaminocycloalkane or a *trans*-(R,R)-1,2-diaminocycloalkane or *trans*-(S,S)-1,2-diaminocycloalkane can be used in this method in combination with any amino acids. This allows the relative stereochemistry of the cycloalkane fused ring and substituent, R_5, R'_5, R_7, R'_7, R_9, R'_9, functionality and stereochemistry to be defined in any manner. As an example *trans*-(R,R)-1,2-diaminocyclhexane was monotosylated and reacted with Boc anhydride to afford the differentiated N-Boc, N-tosyl derivative. The sulfonamide was alkylated with methyl bromoacetate using sodium hydride as the base and saponified to the free acid. The cyclohexanediamine containing N-tosylglycine serves as a dipeptide surrogate in standard solution-phase peptide synthesis. Thus, coupling with a functionalized amino acid ester affords the corresponding pseudo-tripeptide. Two sequential TFA cleavage-couplings affords the pseudo-pentapeptide which can be N- and C-terminus deprotected in one step using HCl/AcOH. DPPA mediated cyclization followed by $LiAlH_4$ or Borane reduction affords the corresponding macrocylic ligand. This ligand system is reacted with a manganese (II) compound, such as manganese (II) chloride under essentially anaerobic conditions to form the corresponding functionalized manganese (II) pentaazacycl alkane complex.

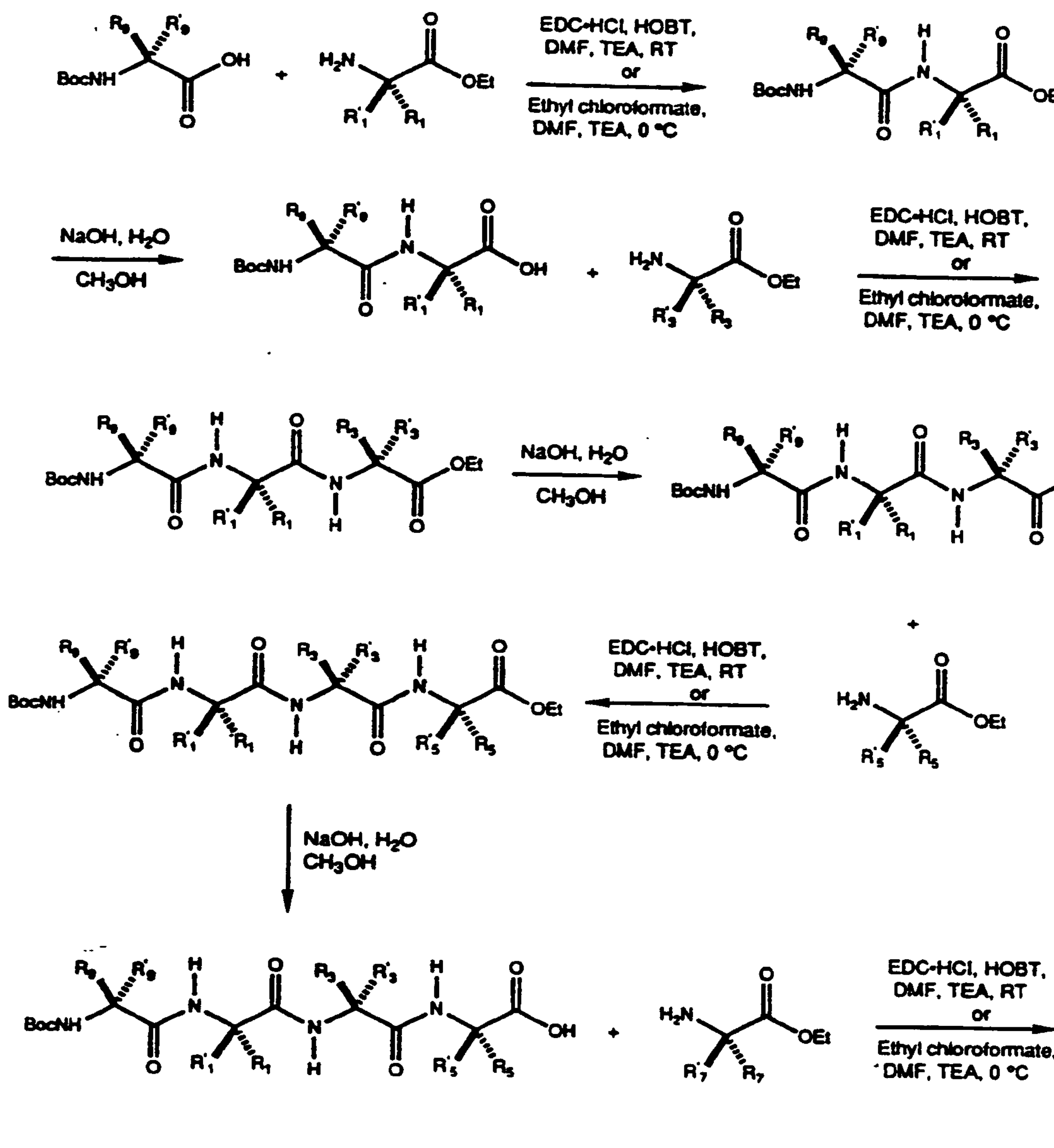
The macrocyclic ligands useful in th complexes of the present invention, wherein R_1, R'_1, R_2, R'_2 and R_5, R'_5, R_6, R'_6, are part of a *cis*- r *trans*- cycl alkyl

ring system and R_9, R'_9 can be H or any functionality previously described, can be prepared according to the iterative pseudo-peptide method shown in Scheme F set forth below. A *cis*-1,2-Diaminocycloalkane or a *trans*-(R,R)-1,2-diaminocycloalkane or *trans*-(S,S)-1,2-diaminocycloalkane can be used in any combination with each other using this method and in combination with any amino acids. This allows the relative stereochemistry of both cycloalkane fused rings and substituent, R_9, R'_9, functionality and stereochemistry to be defined in any manner. Thus, the (S,S)-1,2-diaminocyclohexyl-N-tosylglycine dipeptide surrogate, prepared from (S,S)-1,2-diaminocyclohexane exactly as in Scheme E in the case of (R,R)-1,2-diaminocyclohexane, can be coupled with a functionalized amino acid ester to afford the corresponding pseudo-tripeptide. TFA cleavage affords the pseudo-tripeptide TFA salt which is coupled with (R,R)-diaminocyclohexyl-N-tosylglycine. Saponification and TFA cleavage affords the bis-cyclohexano containing pseudo-pentapeptide. DPPA mediated cyclization followed by $LiAlH_4$ or Borane reduction affords the corresponding bis-cyclohexano-fused macrocylic ligand. This ligand system is reacted with a manganese (II) compound, such as manganese (II) chloride under essentially anaerobic conditions to form the corresponding functionalized manganese (II) pentaazacycloalkane complex.

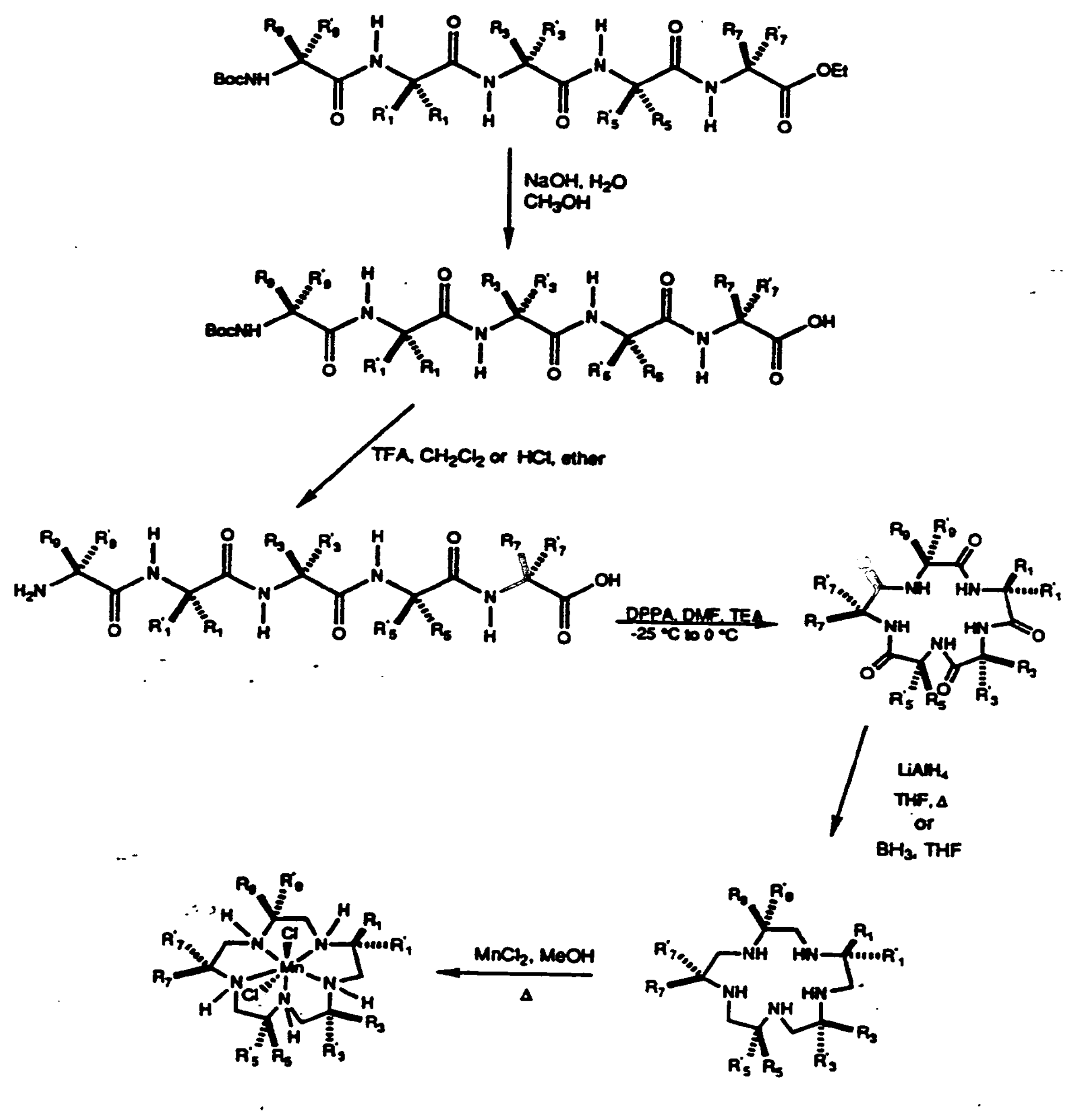
SCHEME A


Scheme A
H2N
N
H
NH2
TsCl, pyridine
TsHN
N
Ts
NHTs
Na/EtOH
TsN
Na+
NTs
OH
TsCl/Et3N
CH2Cl2
OTs
DMF, 100°C
1. H2SO4, 100°C
2. NaOH
MnX2
MeOH
X
Mn

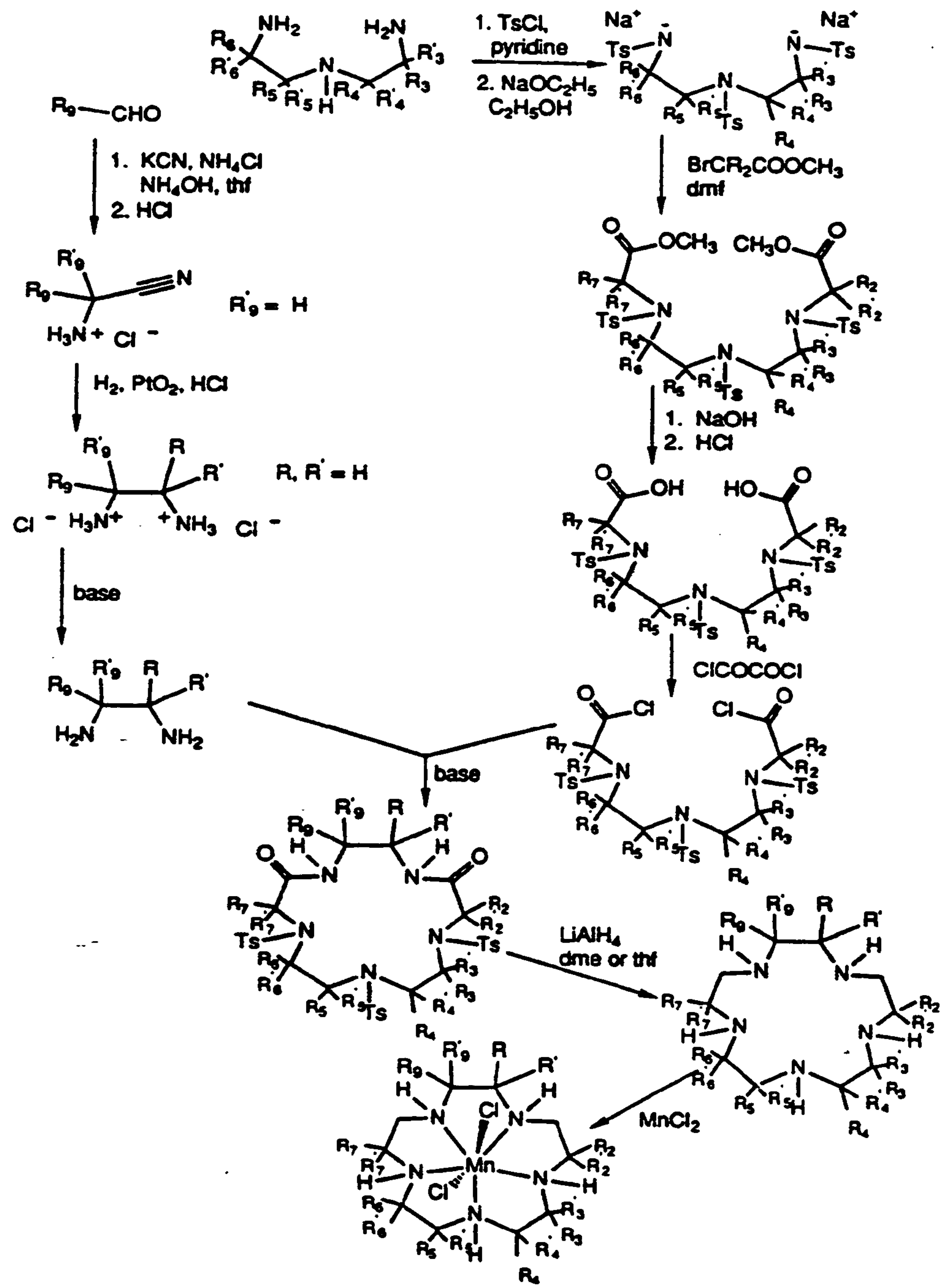
SCHEME B


BocNH
OH
OEt
EDC•HCl, HOBT,
DMF, TEA, RT
or
Ethyl chloroformate,
DMF, TEA, 0 °C
NaOH, H2O
CH3OH

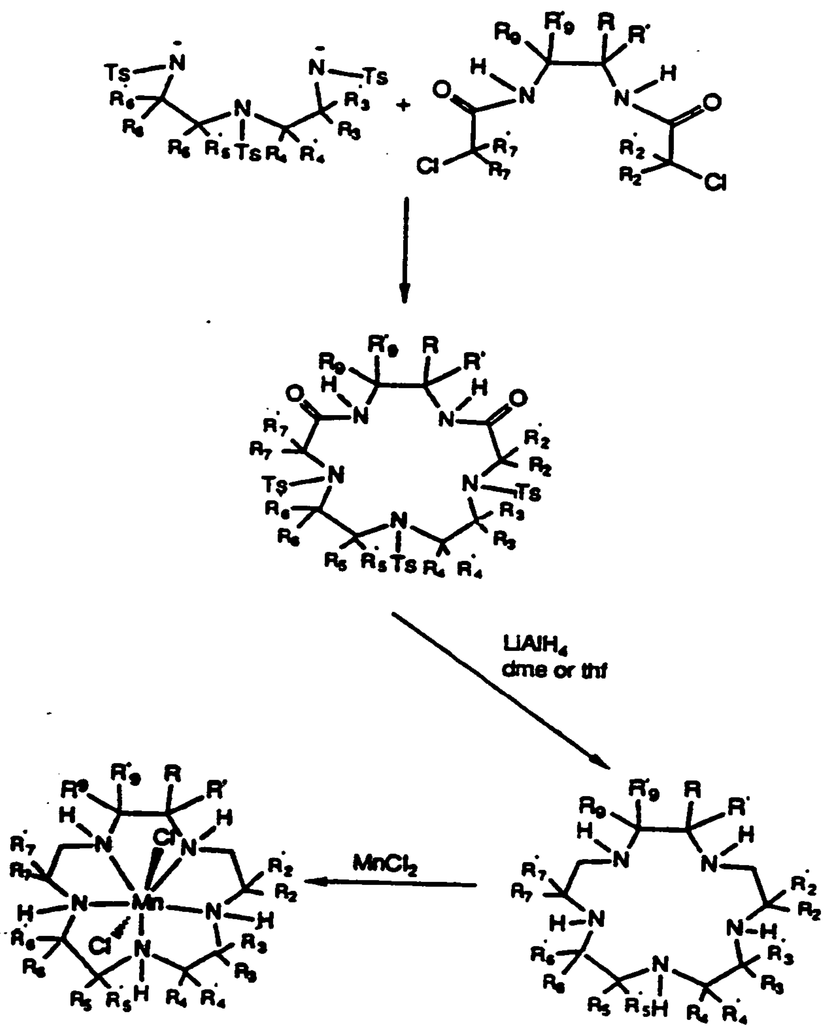
SCHEME B (Con't.)



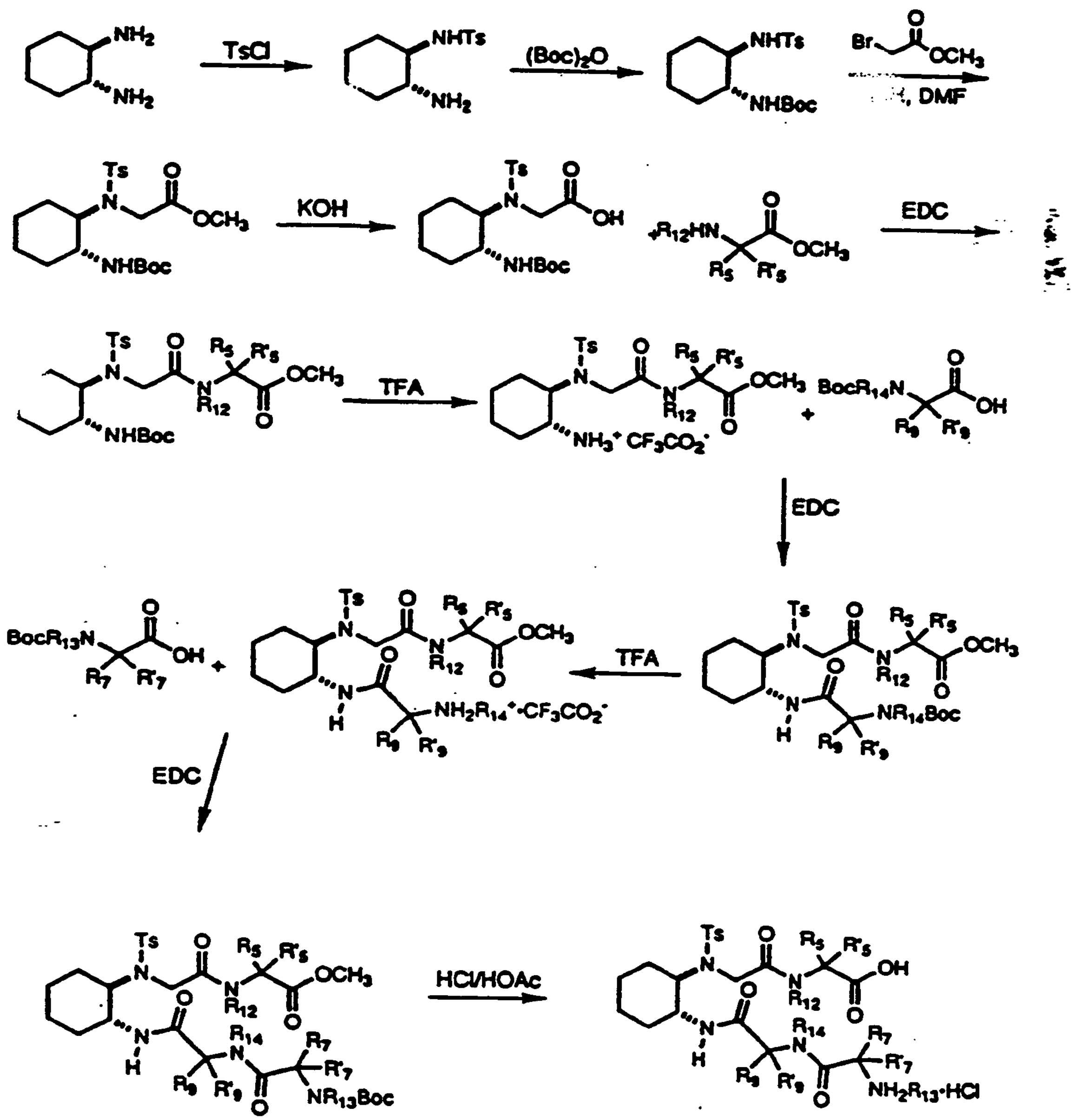
SCHEME C


1. TsCl, pyridine
2. NaOC2H5 C2H5OH
R9—CHO
1. KCN, NH4Cl NH4OH, thf
2. HCl
R'9 = H
H2, PtO2, HCl
R, R' = H
base
BrCR2COOCH3 dmf
1. NaOH
2. HCl
ClCOCOCl
base
LiAlH4 dme or thf
MnCl2

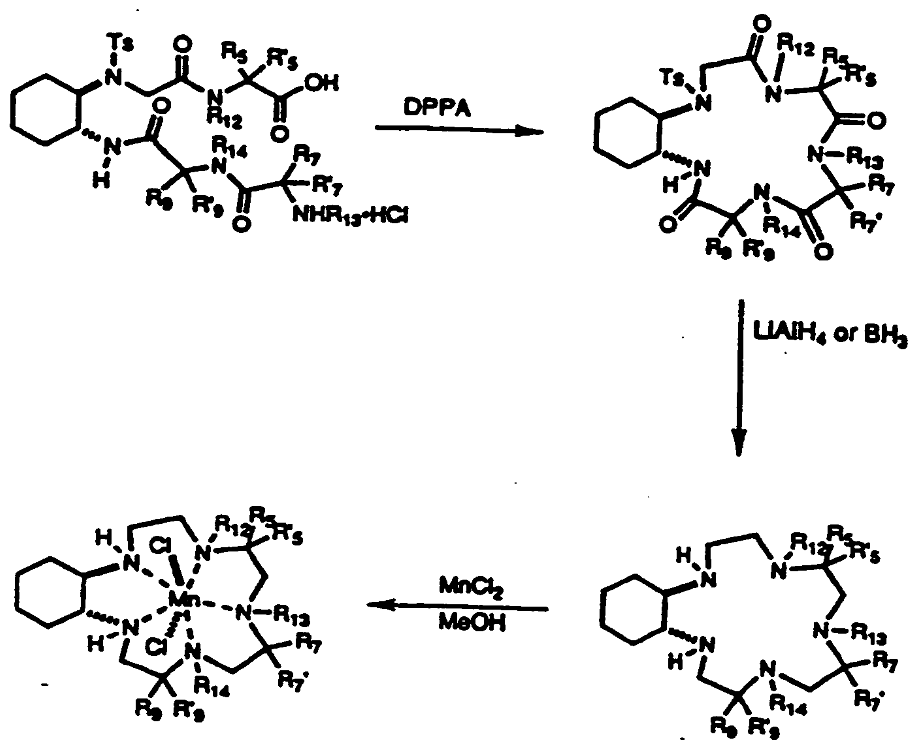
SCHEME D



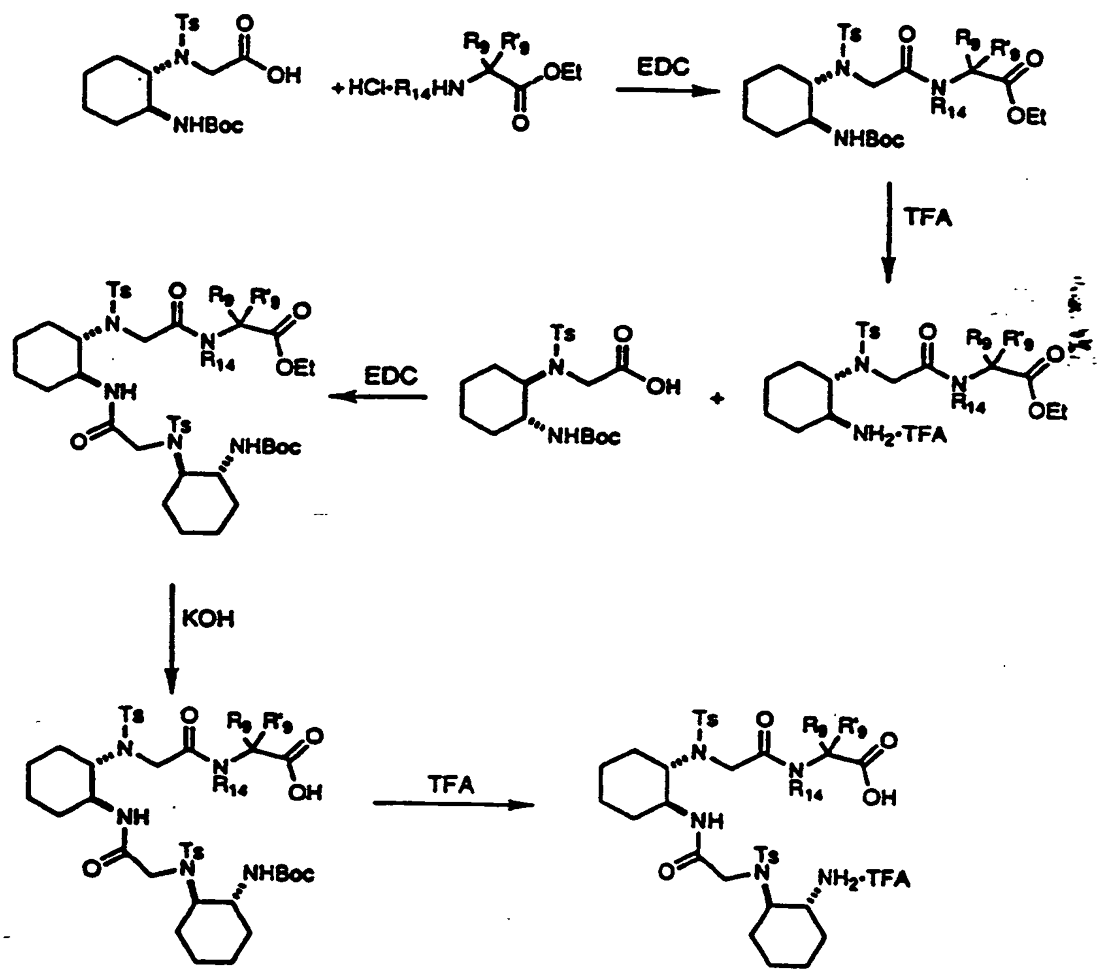
SCHEME E



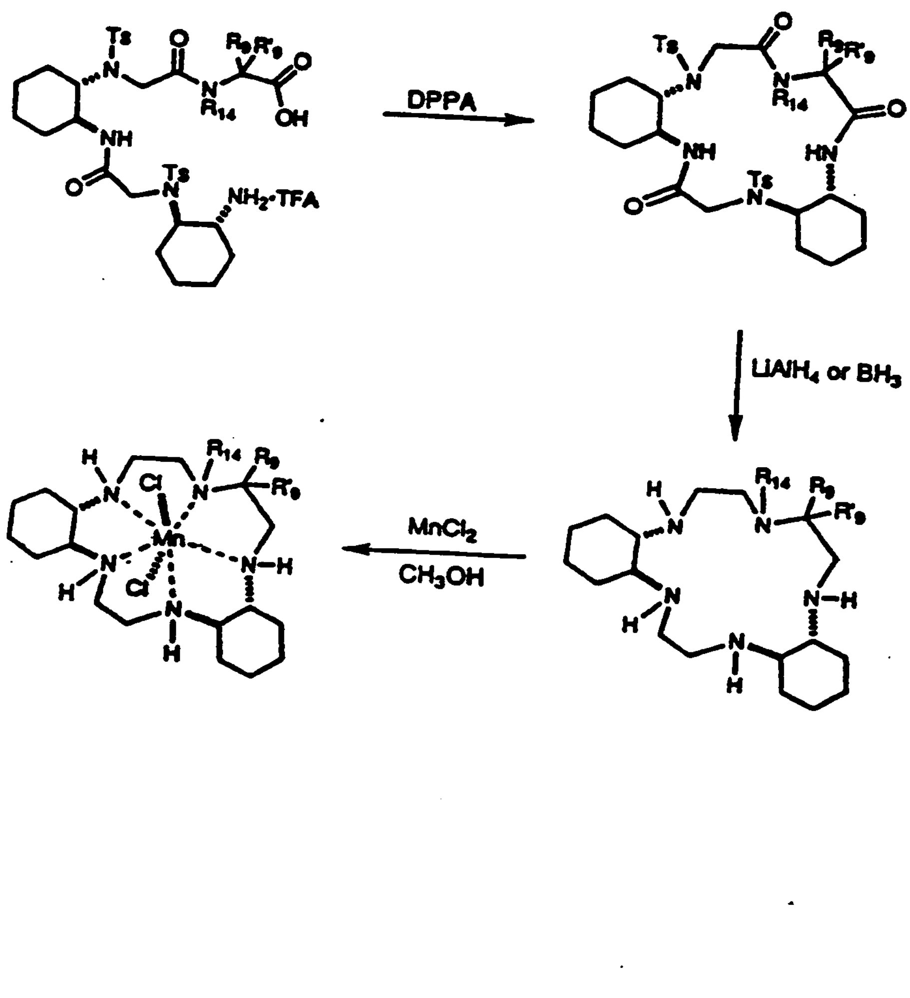
SCHEME E (Con't.)



SCHEME F



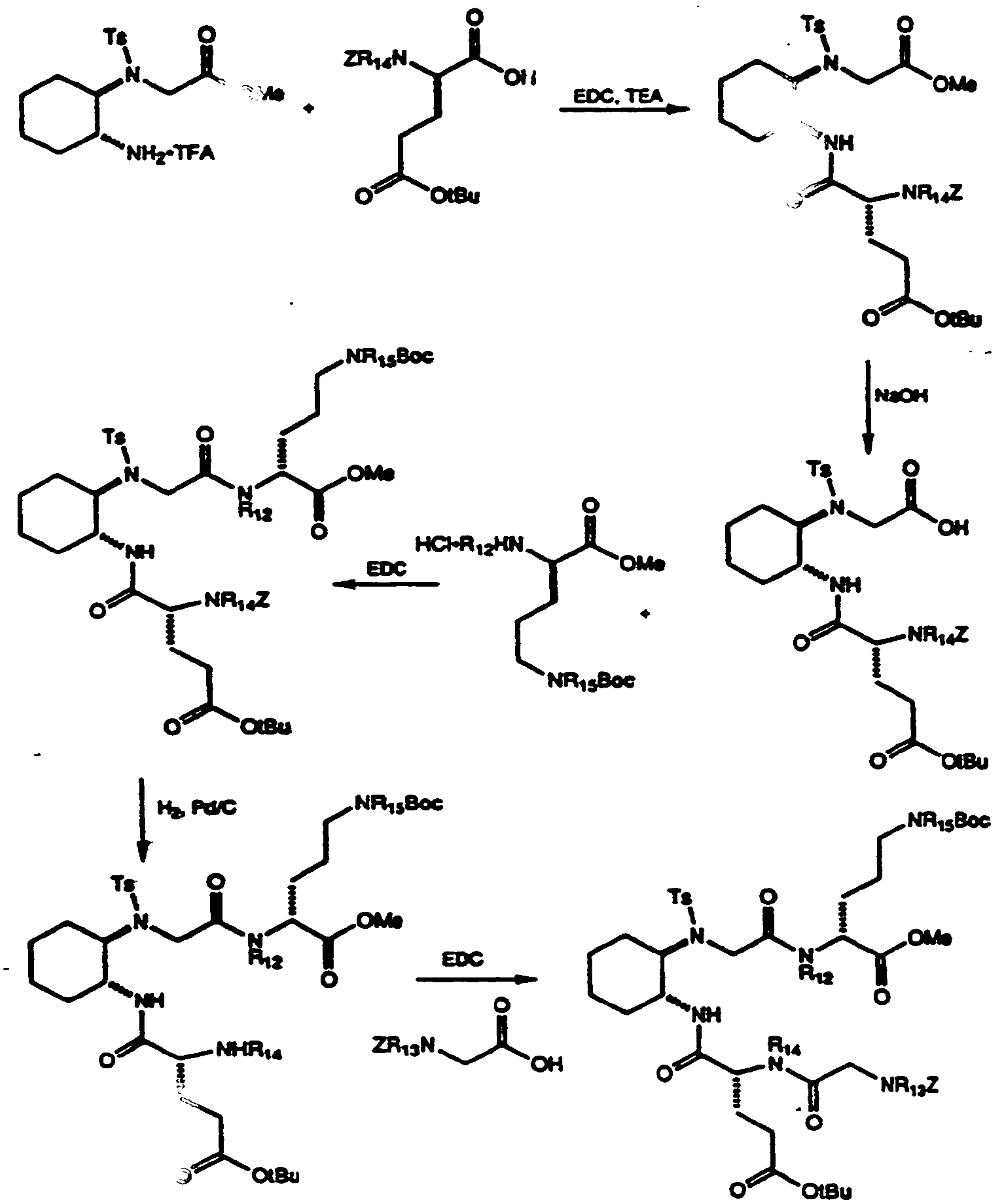
SCHEME F (Con't.)



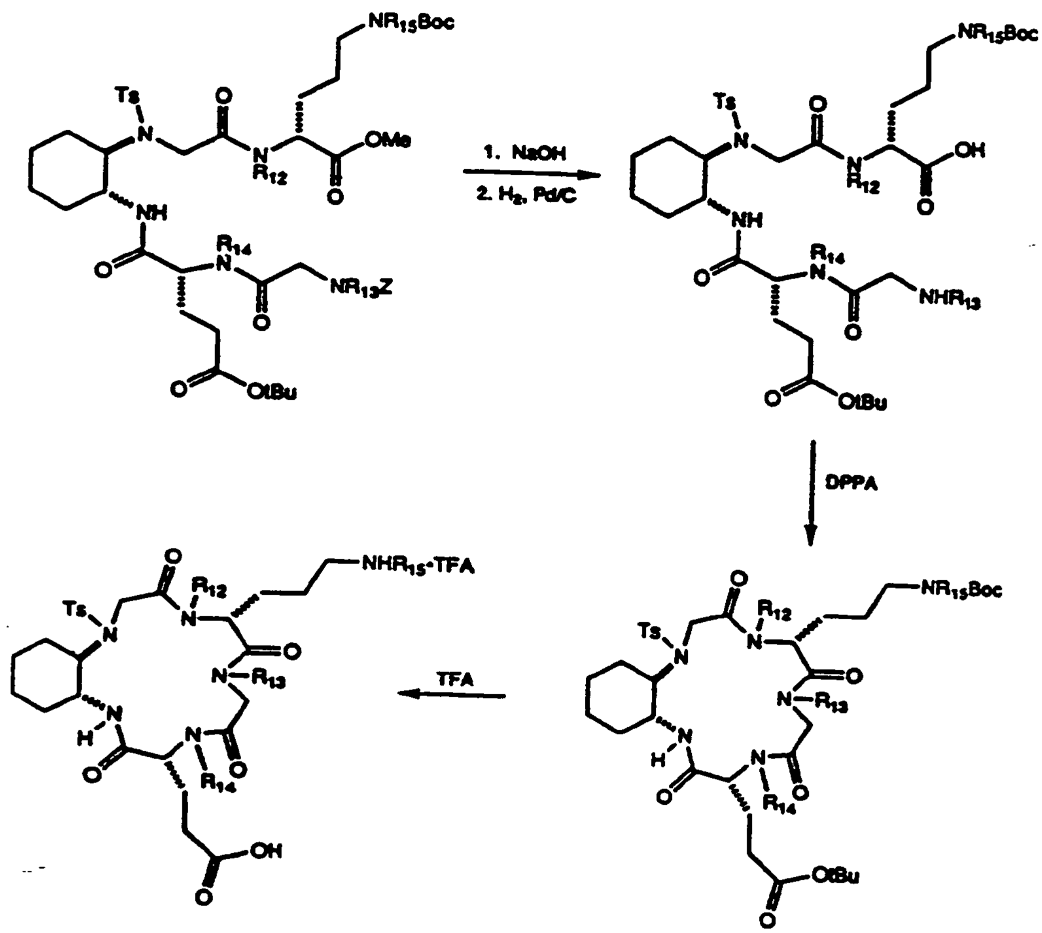
The macrocyclic ligands useful in the preparation of complexes of the present invention containing a strap can be prepared according to the following example schemes.

The macrocyclic ligands useful in the complexes of the present invention, wherein R_4 or R'_4 and R_8 or R'_8 are connected to one another through a "strap" or second ring system in a bicyclic sense, R_{12}, R_{13} and R_{14} can be H or any functionality previously described and R_{17} has the same definition as R_{12}, R_{13} and R_{14} can be prepared according to the method set forth in Scheme G below. The TFA salt of trans-(R,R)-1,2-diaminocyclohexyl-N-tosylglycine dipeptide surrogate is coupled with Z-Glu(OtBu)-OH using EDC in DMF. This tripeptide is then saponified and coupled with Orn(Boc)-OMe•HCl using EDC in DMF. The resulting tetrapeptide is then N-deprotected by hydrogenolysis of the Z group and coupled with Z-Gly again using EDC in DMF. Saponification and hydrogenolysis affords the deprotected pseudopentapeptide which is cyclized with DPPA. The side chains are then deprotected in one step using TFA and a second "strap-cyclization" is effected again with DPPA as the coupling agent. Lithium aluminum hydride reduction affords the bicyclic ligand system which is reacted with manganese (II) chloride under essentially anaerobic conditions to form the corresponding functionalized manganese (II) hexaazabicycloalkane complex.

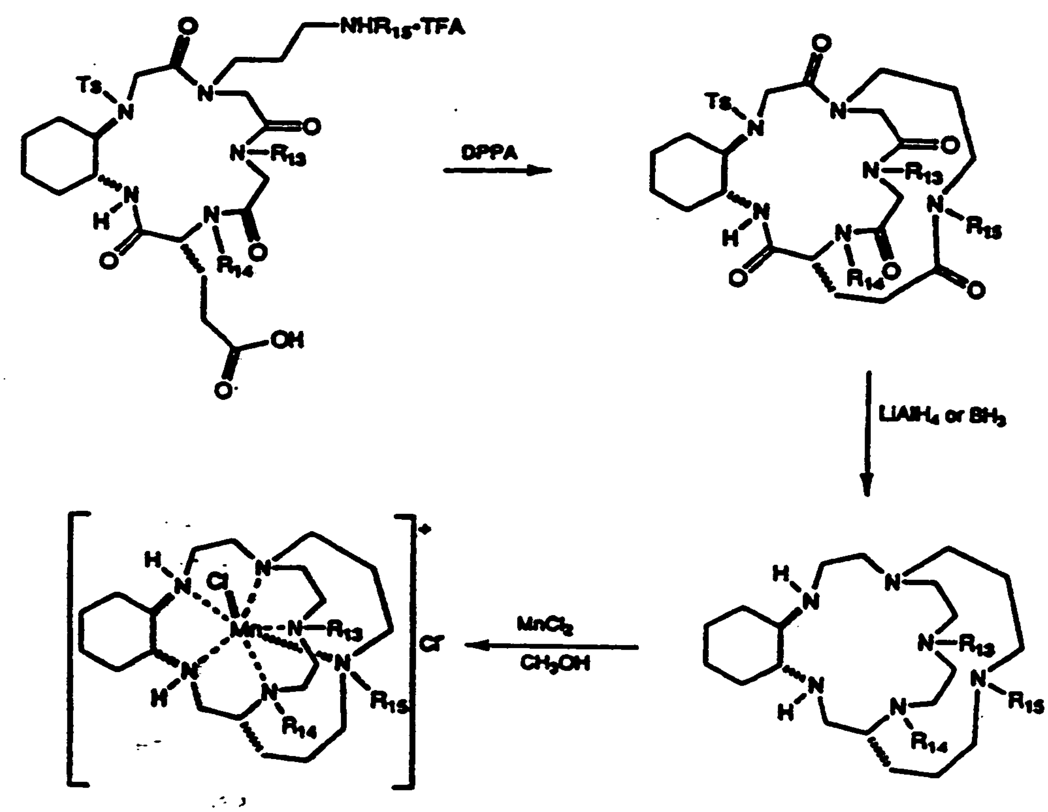
SCHEME G


Ts
NH2•TFA
ZR14N
OH
OtBu
EDC, TEA
OMe
NH
NR14Z
NaOH
HCl•R12HN
NR15Boc
EDC
R12
H2, Pd/C
NHR14
ZR13N
R14
NR13Z

SCHEME G (Con't.)

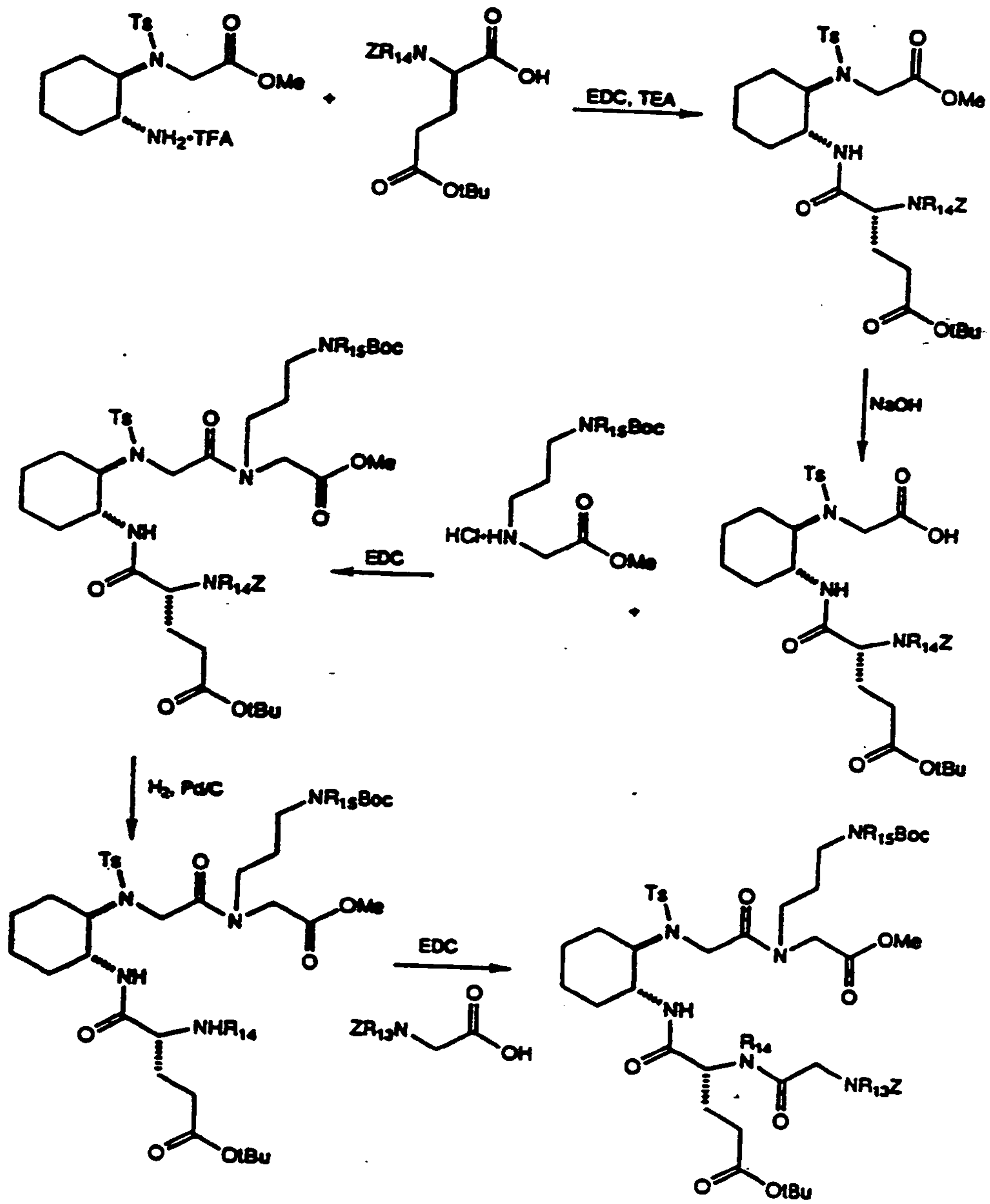


SCHEME G (Con't.)

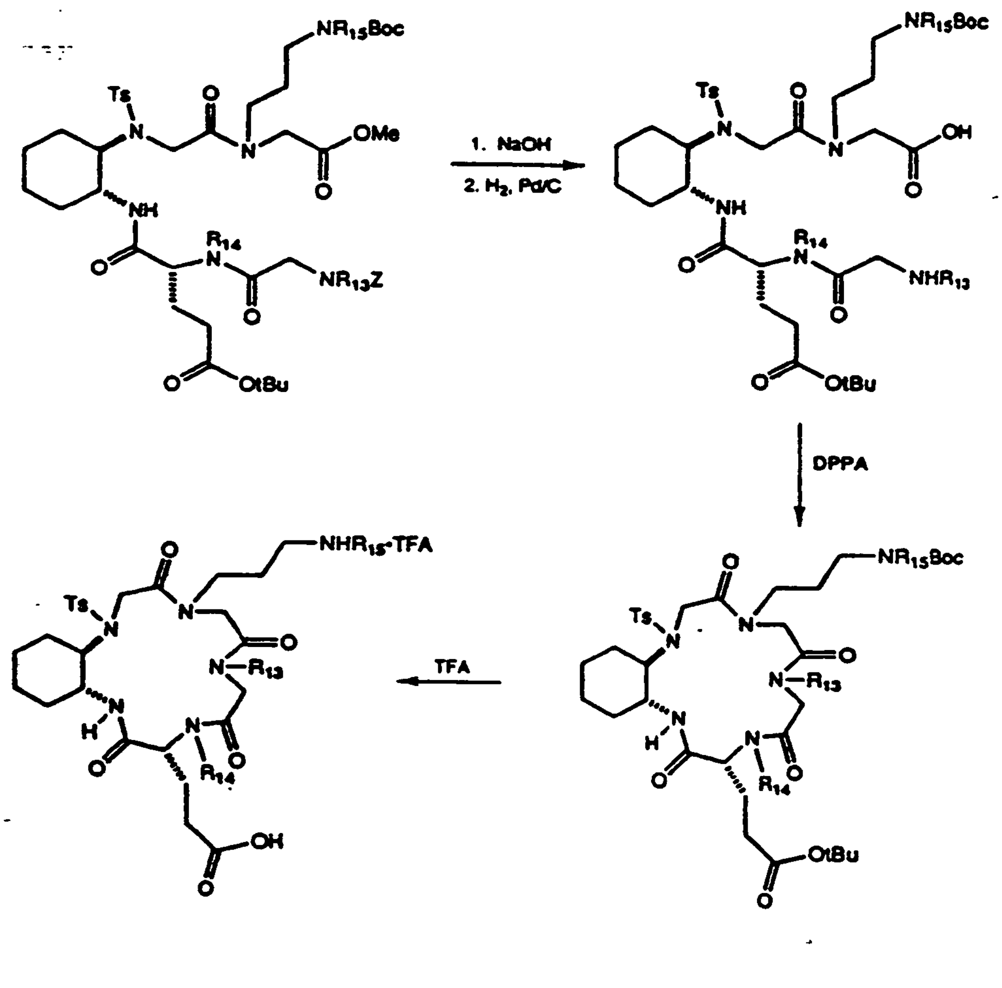


The macrocyclic ligands useful in the complexes of the present invention, wherein nitrogen substituent R_{12} and R_8 or R'_8 are connected to one another through a "strap" or second ring system in a bicyclic sense and R_{13}, R_{14} and R_{17} can be H or any functionality previously described can be prepared according to the method set forth in Scheme H below. The TFA salt of trans-(R,R)-1,2-diaminocyclohexyl-N-tosylglycine dipeptide surrogate is coupled with Z-Glu(OtBu)-OH using EDC in DMF. This tripeptide is then saponified and coupled with N-[3-(Boc-amino)propyl]-Gly-OMe•HCl using EDC in DMF. The resulting tetrapeptide is then N-deprotected by hydrogenolysis of the Z group and coupled with Z-Gly again using EDC in DMF. Saponification and hydrogenolysis affords the deprotected pseudopentapeptide which is cyclized with DPPA. The side chains are then deprotected in one step using TFA and a second "strap-cyclization" is effected again with DPPA as the coupling agent. Lithium aluminum hydride reduction affords the bicyclic ligand system which is reacted with manganese (II) chloride under essentially anaerobic conditions to form the corresponding functionalized manganese (II) hexaazabicycloalkane complex.

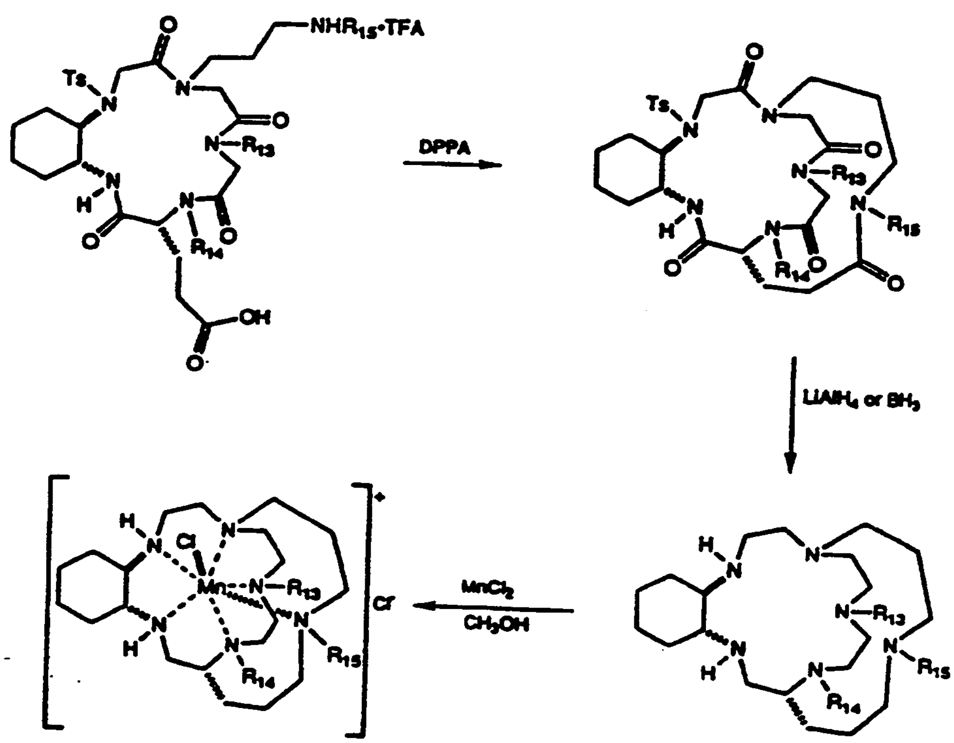
SCHEME H


Ts
N
OMe
NH2·TFA
ZR14N
OH
OtBu
EDC, TEA
NH
NR14Z
NaOH
NR15Boc
HCl·HN
EDC
H2, Pd/C
NHR14
ZR13N
R14
NR13Z

SCHEME H (Con't.)

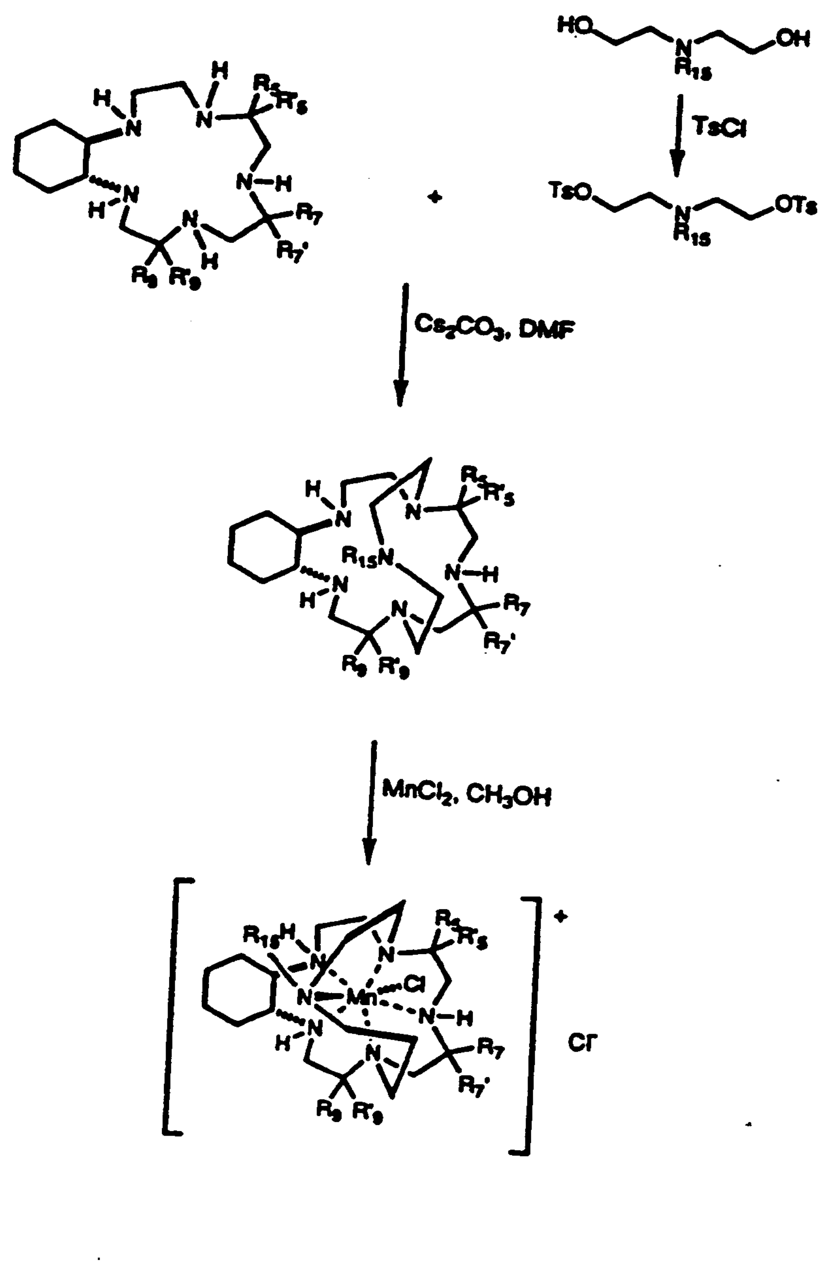


SCHEME H (Con't.)



The macrocyclic ligands useful in the complexes of the present invention, wherein nitrogen substituents R_{12} and R_{14} are connected to one another through a "strap" or second ring system in a bicyclic sense and R_5, R'_5, R_7, R'_7, R_9, R'_9, and R_{17} can be H or any functionality previously described can be prepared according to the method set forth in Scheme I below. The cyclohexyl-containing pentaazamacrocyclic ligand, prepared according to Scheme E is reacted with the ditosyl-sulfonamide of diethanolamine, which is prepared from diethanoamine and tosyl chloride. This "strapping" cyclization can be conducted using Cs_2CO_3 as the base in DMF solvent. This bicyclic ligand system is then reacted with manganese (II) chloride under essentially anaerobic conditions to form the corresponding functionalized manganese (II) hexaazabicycloalkane complex.

SCHEME I


HO
OH
N
R15
TsCl
TsO
OTs
+
Cs_2CO_3, DMF
$MnCl_2$, CH_3OH
R5
R'5
R7
R7'
R9
R'9
R15
Mn
Cl
Cl⁻

The pentaazamacrocycles of the present invention can possess one or more asymmetric carbon atoms and are thus capable of existing in the form of optical isomers as well as in the form of racemic or nonracemic mixtures thereof. The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, for example by formation of diastereoisomeric salts by treatment with an optically active acid. Examples of appropriate acids are tartaric, diacetyltartaric, dibenzoyltartaric, ditoluoyltartaric and camphorsulfonic acid and then separation of the mixture of diastereoisomers by crystallization followed by liberation of the optically active bases from these salts. A different process for separation of optical isomers involves the use of a chiral chromatography column optimally chosen to maximize the separation of the enantiomers. Still another available method involves synthesis of covalent diastereoisomeric molecules by reacting one or more secondary amine group(s) of the compounds of the invention with an optically pure acid in an activated form or an optically pure isocyanate. The synthesized diastereoisomers can be separated by conventional means such as chromatography, distillation, crystallization or sublimation, and then hydrolyzed to deliver the enantiomerically pure ligand. The optically active compounds of the invention can likewise be obtained by utilizing optically active starting materials, such as natural amino acids.

The methods of diagnostic analysis of the present invention involve administering the complexes, i.e. contrast enhancing agents, of the invention to a human or non-human animal subject or host, in an amount sufficient to effect the desired contrast (or shift) and then subjecting the host to diagnostic analysis. Preferably diagn stic analysis is NMR analysis;

including and especially preferred, NMR imaging analysis (or MRI). Further, the complexes of the present invention are useful in diagnostic analysis by X-ray image analysis, ultrasonic analysis or scintigraphic analysis. While described primarily as contrast enhancing agents, the complexes of the invention can act as NMR shift reagents and such use is contemplated by the methods herein.

The complexes of the invention used as contrast enhancing agents are administered in an amount sufficient to effect the desired contrast. For NMR, this amount is an NMR signal effecting amount of the complex, i.e. any amount of said complex that will alter the spin-lattice, spin-spin or spin-echo relaxation times of an NMR signal or for a shift reagent, selectively shift the spectrical position of a resonance nucleus relative to other similar nuclei. This alteration is effected in a manner in order to enhance the signals received from the subject under analysis either by reducing the aforementioned relaxation times or by increasing them with respect to an area of the host or the host per se which has had the complex administered to it. In another embodiment, the NMR signal effecting amount of the complex is that amount which in addition to changing the relaxation times of the NMR signals in the host, will also change such relaxation times sufficiently so that sharper lines of definition or higher contrast is obtained between those parts of the host that have and have not been administered the complex.

The relaxation time T_1 (called the spin-lattice) measures the rate at which magnetic energy is transferred from the resonance nucl i to all ther energetic degrees of fre dom xcluding other r sonance nuclei. The relaxation time T_2 (spin-spin) measures the rate of magnetization transfer to other r sonance nuclei.

Another parameter which can be measured is the density ρ of the protons in the medium. As a first approximation, it represents the quantity of free water contained in the sample.

The image by nuclear magnetic resonance represented the distribution of these parameters ρ, T_1, T_2 or their combination. The contrast between a given tissue and the adjacent tissues increases as a function of the tissues containing more or less water or mobile protons and differing relaxation times. It is also possible to modify the contrast by varying one or more of these parameters (experimentally echoes of spins aiding the function of T_2, or reversal-recovery of the magnetization permitting the local measurement of T_1). Experience has shown that it was of greater interest to modify the relaxation time to improve the contrast of the image which can be accomplished, for example, with the contrast enhancing agents provided herein. The density of the protons (in practice those of water and lipids) varies little between individual organs and often less between normal and pathological tissues. However, the relaxation characteristics are dependent on a larger number of factors (microscopic dynamics of the molecules, chemical exchange, paramagnetic disturbances, etc.) which are much more variable.

A detailed discussion of NMR and theoretical considerations in selecting the appropriate parameters for diagnostic analysis, e.g. MRI, is rendered in U.S. Pat. No. 4,749,560 which is incorporated herein by reference. X-ray image analysis, ultrasonic diagnosis, scintigraphic image analysis and radiotherapy utilizing the complexes of the invention are all conducted in accordance with well-established techniques known to those of ordinary skill in the art.

Moreover, the method of diagnostic analysis of the invention allows tissue or organ-specific diagnostic analysis to be achieved. For example, the contrast enhancing agents can exhibit organ and tissue specificity, e.g. biodifferental distribution, such as in myocardial tissue when the complexes of the invention are lipophilic in nature.

The complexes of the invention may be administered to a host as a pharmaceutical composition in a contrast-enhancing amount. The pharmaceutical compositions contain a contrast-enhancing dosage of the contrast agents according to the invention together with a nontoxic pharmaceutically acceptable carrier, adjuvant or vehicle. The compositions can be administered by well-known routes including oral, intravenous (if soluble), intramuscular, intranasal, intradermal, subcutaneous, parenteral, enteral and the like. Depending on the route of administration, the pharmaceutical composition may require protective coatings.

The pharmaceutical forms suitable for injectable use includes sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the ultimate solution form must be sterile and fluid. Typical carriers include a solvent or dispersion medium containing, for example, water, buffered aqueous solutions (i.e. biocompatable buffers), ethanol, polyol (glycerol, propylene glycol, polyethylene glycol, and the like), suitable mixtures thereof, surfactants or vegetable oils. Sterilization can be accomplished by any art recognized technique, including but not limited to, addition of antibacterial or antifungal agents, for example, paraben, chlorobutan 1, phen 1, s rbic acid, thimerosal, and the like. Further, isotonic agents,

such as sugars or sodium chloride may be incorporated in the subject compositions.

Production of sterile injectable solutions containing the subject contrast agent is accomplished by incorporating these agents in the required amount in the appropriate solvent with various ingredients enumerated above, as required, followed by sterilization, preferably filter sterilization. To obtain a sterile powder, the above solutions are vacuum-dried or freeze-dried as necessary.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, granules and gels. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as in normal practice, additional substances other than inert diluent, e.g. lubricating agents such as magnesium stearate. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluent commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

The contrast agents of the inventions are thus compounded for convenient and effective administration in pharmaceutically effective amounts with a suitable pharmaceutically acceptable carrier, adjuvant or vehicle in a dosage which effects contrast enhancement. These amounts ar preferably about 1 µmol to 1 m l of the c ntrast agent per liter and/or administered in doses of about 0.001 t 5 mmol/kg body weight. Preferred

compositions provide effective dosages of contrast agents in the range of about 0.001-5 mmol/kg for NMR diagnostics, preferably about 0.005-0.5 mmol/kg; in the range of about 0.1-5 mmol/kg for X-ray diagnostics; and in the range of about 0.1-5 mmol/kg for ultrasound diagnostics. For scintigraphic diagnostics, the dose of the contrast agent should generally be lower than for NMR diagnostics, e.g. MRI. For radiotherapy, conventional doses known to those of ordinary skill in the art can be used.

As used herein, a pharmaceutically acceptable carrier, adjuvant or vehicle includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic agents, and the like. The use of such media and agents are well known in the art.

Contemplated equivalents of the general formulas set forth above for the compounds and derivatives as well as the intermediates are compounds otherwise corresponding thereto and having the same general properties such as tautomers of the compounds and such as wherein one or more of the various R groups are simple variations of the substituents as defined therein, e.g., wherein R is a higher alkyl group than that indicated, or where the tosyl groups are other nitrogen or oxygen protecting groups or wherein the O-tosyl is a halide. Anions having a charge other than 1, e.g., carbonate, phosphate, and hydrogen phosphate, can be used instead of anions having a charge of 1, so long as they do not adversely affect the overall activity of the complex. However, using anions having a charge other than 1 will result in a slight modification of the general formula for the complex set forth above. In additi n, where a substituent is designated as, or can be, a hydrogen, the exact chemical nature of a substituent which is other than hydrogen at that position, .g., a hydrocarbyl radical r a halogen,

hydroxy, amin and the like functional group, is not critical so long as it does not adversely affect the overall activity and/or synthesis procedure.

The chemical reactions described above are generally disclosed in terms of their broadest application to the preparation of the compounds of this invention. Occasionally, the reactions may not be applicable as described to each compound included within the disclosed scope. The compounds for which this occurs will be readily recognized by those skilled in the art. In all such cases, either the reactions can be successfully performed by conventional modifications known to those skilled in the art, e.g., by appropriate protection of interfering groups, by changing to alternative conventional reagents, by routine modification of reaction conditions, and the like, or other reactions disclosed herein or otherwise conventional, will be applicable to the preparation of the corresponding compounds of this invention. In all preparative methods, all starting materials are known or readily preparable from known starting materials.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

EXAMPLES

All reagents were used as received without purification unless otherwise indicated. All NMR spectra were obtained n a Varian VXR-300 or VXR-400 nucl ar magnetic resonance spectr meter. Qualitative and quantitative mass spectrosc py was run on a Finnigan

MAT90, a Finnigan 4500 and a VG40-250T using m-nitrobenzyl alcohol(NBA) or m-nitrobenzyl alcohol/LiCl (NBA+Li). Melting points (mp) are uncorrected.

The following abbreviations relating to amino acids and their protective groups are in accordance with the recommendation by IUPAC-IUB Commission on Biochemical Nomenclature (Biochemistry, 11, 1726 (1972)) and common usage.

Ala	L-Alanine
DAla	D-Alanine
Gly	Glycine
Ser	L-Serine
DSer	D-Serine
Ppg	Propargylglycine
Tyr	L-Tyrosine
Bzl	Benzyl
Boc	*tert*-Butoxycarbonyl
Et	Ethyl
TFA	Trifluoroacetate
DMF	Dimethylformamide
HOBT•H_2O	1-Hydroxy-(1*H*)-benzotriazole monohydrate
EDC•HCl	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
TEA	Triethylamine
DMSO	Dimethylsulfoxide
THF	Tetrahydrofuran
DPPA	Diphenylphosphoryl azide
DMPU	Dimethylpropyleneurea
c	concentration, g/cc
DME	1,2-Dimethoxyethane

The abbreviation Cyc represents 1,2-cycl hexanediamine (stereochemistry, i.e. R,R or S,S, is indicated as such). This allows thr e letter code

peptide nomenclature to be used in pseudopeptides containing the 1,2-cyclohexane diamine "residue".

Example 1 (Comparative)

A. Synthesis of 1,4,7-Tris(p-toluenesulfonyl)-1,4,7-triazaheptane

This compound was synthesized following the procedure of Atkins, T. J.; Richman, J.E.; and Oettle, W.F.; *Org. Synth.*, 58, 86-98 (1978). To a stirred solution of p-toluenesulfonyl chloride (618 g, 3.24 mole) in pyridine (1500 ml) at 0°C was added a solution of 1,4,7-triazaheptane (95.5 g, 0.926 mole) in pyridine (150 ml) under a dry argon atmosphere, maintaining the temperature ≤ 50°C. The addition required 30 minutes. After the mixture was allowed to cool to room temperature slowly while stirring for 3 h, H_2O(2 l) was slowly added to the cooled (ice bath) mixture. The heavy white precipitate which formed was filtered and washed thoroughly with H_2O. The pale yellow solid was dissolved in DMF (3 l) and 0.1 N HCl (4 l) was slowly added at 5°C. The slurry was filtered and the pale yellow solid was washed thoroughly with H_2O and dried in vacuo to give 486 g (93% yield) of the product: mp 180-1°C; ^{1}H NMR(DMSO-d_6) δ 2.39 (s,3 H), 2.40 (s, 6 H), 2.84 (m, 4 H), 3.04 (t, J=6.9 Hz, 4 H) 7.40 (d, J=8.1 Hz, 4 H), 7.59 (d, J=8.3 Hz, 2 H), 7.67 (m, 6 H).

B. Synthesis of 1,4,7-Tris(p-toluenesulfonyl)-1,4,7-triazaheptane-1,7-disodium Salt

This compound was synthesized following the procedure of Atkins, T.J.; Richman, J.E., and Oettle, W.F.; *Org. Synth.*, 58 86-98 (1978). To a mechanically stirred slurry of 1,4,7-tris(p-toluenesulfonyl)-1,4,7-triazaheptane prepared as in Exampl 1A (486 g, 0.859 mole) in ethanol (1150 ml) heated to reflux under a dry argon atmosphere was added a solution of sodium ethoxide

(prepared by dissolving sodium metal (39.5 g, 1.72 mole) in absolute ethanol (1.0 l)) as rapidly as possible. The clear brown solution which formed rapidly was allowed to cool to room temperature and ethyl ether (1.0 l) was added. The crystals were filtered under a dry argon blanket, washed with 3:1 ethanol:ethyl ether and ethyl ether. The crystals were then dried in vacuo to give 509 g (97% yield) of the product as a white powder: ^1H NMR (DMSO-d_6) δ 2.30 (s 6 H), 2.36 (s, 3 H), 2.63 (t, J=8.7 Hz, 4 H), 2.89 (t, J=7.2 Hz, 4 H) 7.11 (d, J=8.1 Hz, 4 H), 7.28 (d, J=8.0 Hz, 2 H), 7.46 (m, 6 H).

<u>C. Synthesis of 3,6-Bis(p-toluenesulfonyl)-3,6-diazaoctane-1,8-di-p-toluenesulfonate</u>

To a stirred solution of p-toluenesulfonyl chloride (566 g, 2.97 mole) and triethylamine (300 g, 2.97 mole) in CH_2Cl_2 (2.0 l) at 0°C under a dry argon atmosphere was added 3,6-diazaoctane-1,8-diol (100 g, 0.675 mole) in portions, maintaining the temperature <10°C. The addition required 30 minutes. The mixture was allowed to warm to room temperature while stirring an additional 18 h and was then poured onto ice (1000 g). The CH_2Cl_2 layer was separated, washed with 10% HCl, H_2O and saturated NaCl solution, and dried ($MgSO_4$). The solution was concentrated in vacuo to a volume of 1.5 l. Crystallization by the addition of hexane (4 l) gave 477 g (92% yield) of the product as colorless needles: mp 151-3°C; ^1H NMR ($CDCl_3$) δ 2.43 (s, 12 H), 3.29 (s, 4 H), 3.36 (t, J=5.2 Hz, 4 H), 4.14 (t, J=5.2 Hz, 4 H), 7.33 (d, J=7.8 Hz, 8 H), 7.71 (d, J=8.2 Hz, 4 H), 7.79 (d, J=8.3 Hz, 4 H).

<u>D. Synthesis of 1,4,7,10,13-Penta(p-toluenesulfonyl)-1,4,7,10,13-pentaazacyclopentadecane</u>

This c mpound was synthesized following the procedure f Richman, J.E., and Atkins, T.J., *J. Am. Ch m. Soc.*, <u>96</u>, 2268-70 (1974). T a stirred s lution of 1,4,7-tris(p-toluenesulfonyl)-1,4,7-triazaheptan -

1,7-disodium salt prepared as in Example 1B (146 g, 0.240 mole) in anhydrous DMF (2250 ml) was added dropwise over 3 h to a solution of 3,6-bis(p-toluenesulfonyl)-3,6-diazaoctane-1,8-di-p-toluenesulfonate prepared as in Example 1C (184 g, 0.240 mole) in anhydrous DMF (1020 ml) under a dry argon atmosphere, maintaining the temperature at 100°C. After stirring an additional 1 h at 100°C, the solution was concentrated in vacuo to a volume of 1.5 l. H_2O (500 ml) was slowly added at 80°C to crystallize the product. The resulting slurry was slowly cooled to 0°C and additional H_2O (1250 ml) added. The solid was filtered, washed thoroughly with H_2O and then 90% ethanol and dried in vacuo. The off-white solid was dissolved in CH_2Cl_2, insoluble impurities were removed by filtration and the filtrate was washed with H_2O and then dried ($MgSO_4$). The solvent was removed in vacuo to give a yellow solid which was purified by recrystallization from CH_2Cl_2-hexane to give 164 g (69% yield) of the product as a white crystalline solid: mp 290-3°C; ^1H NMR ($CDCl_3$) δ 2.44 (s, 15 H) 3.27 (s, 20 H), 7.32 (d, J=8.3 Hz, 10 H), 7.66 (d, J=8.3 Hz, 10 H).

E. Synthesis of 1,4,7,10,13-Pentaazacyclopentadecane

A mixture of 1,4,7,10,13-penta(p-toluenesulfonyl)-1,4,7,10,13-pentaazacyclopentadecane prepared as in Example 1D (168 g, 0.170 mole) and concentrated H_2SO_4 (500 ml) was heated at 100°C with stirring under a dry argon atmosphere for 70 h. To the resulting dark brown solution ethanol (500 ml) was added dropwise with stirring at 0°C followed by ethyl ether (3 l). The white solid was filtered and washed with ethyl ether. The solid was then dissolved in H_2O (500 ml) and the resulting solution washed with ethyl ether. Upon reducing the volume of the solution in vacuo to 200 ml, the pH was adjusted to 10-11 with 10 N NaOH and the solvent was remov d in vacuo. Ethan 1 (500 ml) was then

added and removed in vacuo to dryness. The resulting tan oily solid was extracted with hot THF (2x500 ml) and filtered at room temperature. The filtrates were combined and the solvent removed in vacuo to give the crude product as a yellow crystalline solid which was then redissolved in CH_3CN and filtered to remove insoluble impurities. Recrystallization from cold (-20°C) CH_3CN gave 11.3 g (31% yield) of the product as colorless needles: mp 108-9°C; ^1H NMR ($CDCl_3$) δ 1.74 (br s, 5 H), 2.73 (s, 20 H); Exact mass $(M+Li)^+$: calcd, 222.2270; Found, 222.2269 ($C_{10}H_{25}N_5Li$).

F. Synthesis of [Manganese(II)dichloro(1,4,7,10,13-Pentaazacyclopentadecane)]

A solution of 1,4,7,10,13-pentaazacyclopentadecane prepared as in Example 1E (2.0 g, 9.3 mmole) and anhydrous manganese(II) chloride (1.2 g, 9.3 mmole) in anhydrous methanol (50 ml) was refluxed under a dry nitrogen atmosphere for 3 h. The solution was filtered and the solvent removed in vacuo. The resulting solid was recrystallized from ethanol-ethyl ether to give 2.79 g (88% yield) of the product as an off-white crystalline solid: FAB mass spectrum (NBA) m/z (relative intensity) 340 (M^+, 2), 305/307 ($(M-Cl)^+$ 100/45)); Anal. Calcd. for $C_{10}H_{25}Cl_2MnN_5$: C, 35.17; H, 7.38; Cl, 20.76; N 20.60. Found: C, 34.95; H, 7.31; Cl, 20.49; N, 20.22.

Example 2

A. Synthesis of Dimethyl 3,6,9-Tris(p-toluenesulfonyl)-3,6,9-triazaundecanedioate

1,4,7-Tris(p-toluenesulfonyl)-1,4,7-triazaheptane-1,7-disodium salt prepared as in Example 1B (30 g, 49.2 mmol) was diss lved in dry N,N-dimethylf rmamide (180 ml) under arg n. After c oling t 0° C in an ice bath, methyl chloroacetate (15.40 g, 141.9 mm l) was added dropwise over a 10 min period. The reaction mixture

became cloudy at the end of the addition, and was allowed to stir overnight while the ice bath warmed to room temperature. The solvent was evaporated under reduced pressure to give a brown oil which was dissolved in ethyl acetate (450 ml) giving a milky solution. This solution was washed twice with water (500 ml, then 300 ml). The combined water layers were back extracted with ethyl acetate (300 ml). The combined ethyl acetate layers were washed twice with saturated sodium chloride solution (200 ml), filtered, and evaporated to dryness. This residue was dissolved in dichloromethane (200 ml) and evaporated to dryness, and placed on the vacuum line. After recrystallization from chloroform-methanol, and washing with methanol and ether, an off-white solid was obtained weighing 27.46 g. An additional quantity of a slightly darker solid (4.7 g) was recovered from the filtrate after removing the solvent and recrystallizing as before. Total yield was 32.2 g (93% yield): mp 141-2° C; ^{1}H NMR ($CDCl_3$) δ 2.42 and 2.44 (2 s, 9 H), 3.41 (br s, 8 H), 3.60 (s, 6 H), 4.07 (s, 4 H), 7.26 - 7.35 (m, 6 H), 7.[illegible]3 - 7.74 (m, 6 H).

<u>B. Synthesis of 3,6,9-Tris(p-toluenesulfonyl)-3,6,9-triazaundecanedioic Acid</u>

Dimethyl 3,6,9-tris(p-toluenesulfonyl)-3,6,9-triazaundecanedioate prepared as in Example 2A (16 g, 22.5 mmol) was slurried in tetrahydrofuran (100 ml). Sodium hydroxide (2 N, 160 ml) was added dropwise over a 1 h period. After 72 h, the solvent was evaporated under reduced pressure, and hydrochloric acid (1 N) was added to lower the pH to 4. This aqueous phase was extracted several times with ethyl acetate. The combined ethyl acetate layers were washed twice with brine, dried ($MgSO_4$), filtered, and evaporated to give a white solid, 14.22 g (93% yield): mp 177-80° C; ^{1}H NMR (DMSO-d_6) δ 2.38 and 2.40 (2 s, 9 H), 3.10 (m, 4 H), 3.29 (m, 4 H), 3.73 (s, 4 H), 7.37 and 7.41 (2 d, J =

7.9, 8.2 Hz, 6 H), 7.61 and 7.66 (2 d, J = 8.2 , 8.0 Hz, 6 H).

C. Synthesis of 3,6,9-Tris(p-toluenesulfonyl)-3,6,9-triazaundecanedioyl Dichloride

3,6,9-Tris(p-toluenesulfonyl)-3,6,9-triazaundecanedioic acid prepared as in Example 2B (40.5 g, 59.4 mmol) was placed in a round bottom flask under argon, and oxalyl chloride (400 g, 3.15 moles) was added. This mixture, initially cloudy, became clear after a few hours, and was stirred overnight at room temperature. At the end of this time it was heated to 40° C for 30 min. Oxalyl chloride was removed on the rotary evaporator. Dichloromethane (50 to 60 ml) was added to dissolve the resulting solid, and was removed on the rotary evaporator. This process was repeated twice, giving 40.5 g (99% yield) of a white solid: mp 136-7° C; ^{1}H NMR ($CDCl_3$) δ 2.43 and 2.46 (2 s, 9 H), 3.30 - 3.38 (m, 4 H), 3.40 - 3.48 (m, 4 H), 4.56 (s, 4 H), 7.30 - 7.40 (m, 6 H), 7.71 (d, J = 8.2 Hz, 6 H).

D. Synthesis of *trans*-5,6-Cyclohexano-1,10,13-tris(*p*-toluenesulfonyl)-1,4,7,10,13-pentaazacyclopentadecan-3,8-dione

Dry dichloromethane (150 ml) was placed in a one liter four necked round bottom flask under argon equipped with two dropping funnels. 3,6,9-Tris(*p*-toluenesulfonyl)-3,6,9-triazaundecanedioyl dichloride prepared as in Example 2C (5.07 g, 7.05 mmol) was dissolved in dry dichloromethane (150 ml) and added to one of the dropping funnels. *trans*-1,2-Diaminocyclohexane (0.805 g, 7.05 mmol) and triethylamine (1.96 ml, 14.1 mmol) were dissolved in dry dichloromethane (150 ml) and added to the other dropping funnel. After cooling the dichlorom thane containing flask in an ice bath to an internal t mperature of 0 to 5° C, the contents of the dropping funnels were added

simultaneously t the stirred solution over 2.25 h. A white precipitate was evident before the addition was finished. At the end of this time, the ice bath was removed and the reaction mixture was stirred overnight at room temperature. The reaction mixture was filtered and the white precipitate was identified as pure product. The filtrate was washed twice with water (100 ml), once with saturated sodium chloride solution (100 ml), dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. Recrystallization from dichloromethane-hexane provided additional product, along with the initial precipitate for a total of 2.85 g (53% yield); mp 254-5° C; ^{1}H NMR (DMSO-d_6) δ 1.15 (br s, 4 H), 1.52 - 1.75 (m, 4 H), 2.42 and 2.43 (2 s, 9 H), 3.04 (m, 8 H), 3.51 (d + m, J = 16.5 Hz, 4 H), 4.01 (d, J = 16.5 Hz, 2 H), 7.35 - 7.53 (m, 8 H), 7.71 (d, J = 8.3 Hz, 4 H), 7.80 (br d, J = 10.5 Hz, 2 H).

E. Synthesis of *trans*-1,2-Bis(chloroacetamido)cyclohexane

A 12 liter three-neck flask equipped with a magnetic stirbar and two 1 liter dropping funnels was charged with 1,2-diaminocyclohexane (35.0 g, 0.310 mol) dissolved in chloroform (375 ml) and water (185 ml). The two dropping funnels were charged individually with chloroacetyl chloride (75 ml, 0.94 mol) in chloroform (440 ml) and potassium carbonate (120.5 g, 0.87 mol) in water (4 l), added in four portions during the addition. The flask was cooled in an ice salt bath and addition of the reagents was carried out over 2 h. The ice salt bath was removed, water (600 ml) was added, and the reaction mixture was stirred for 2.5 h. The mixture was separated and the water layer was extracted with chloroform several times. The combined chlor form layers were washed with water and th n brine. The organic layer was dried (sodium sulfate) and

concentrated in vacuo to yield an off-white solid. The solid was washed with ether to yield 55.32 g (67% yield) of a white solid after drying in vacuo: mp 202-3° C; ^{1}H NMR ($CDCl_3$) δ 1.27 - 1.50 (m, 4 H), 1.75 - 1.95 (m, 2 H), 2.03 - 2.20 (m, 2 H), 3.72 - 3.87 (m, 2 H), 4.05 (s, 4 H), 6.81 (br s, 2 H).

F. Synthesis of *trans*-5,6-Cyclohexano-1,10,13-tris(p-toluenesulfonyl)-1,4,7,10,13-pentaazacyclopentadecan-3,8-dione (alternate method)

A 5 liter three-neck flask equipped with a magnetic stir bar and 1 liter dropping funnel was dried and placed under a dry argon atmosphere. A solution of *trans*-1,2-bis(chloroacetamido)cyclohexane prepared as in Example 2E (6.68 g, 250 mmol) in anhydrous DMF (1.25 l) was added to a solution of 1,4,7-tris(p-toluenesulfonyl)-1,4,7-triazaheptane-1,7-disodium salt prepared as in Exa le 1B (15.2 g, 250 mmol) in anhydrous DMF (1.2) at room temperature over a period of 12 h. After stirring an additional 2 h, the solvent was removed in vacuo. The solid residue was triturated with chloroform (1 l) and filtered to yield a white solid. The solid was recrystallized from acetonitrile to give 7.22 g (38% yield) of fluffy white crystals: mp 254-5° C; ^{1}H NMR (DMSO-d_6) δ 1.15 (br s, 4 H), 1.52 - 1.75 (m, 4 H), 2.42 and 2.43 (2 s, 9 H), 3.04 (m, 8 H), 3.51 (d + m, J = 16.5 Hz, 4 H), 4.01 (d, J = 16.5 Hz, 2 H), 7.35 - 7.53 (m, 8 H), 7.71 (d, J = 8.3 Hz, 4 H), 7.80 (br d, J = 10.5 Hz, 2 H).

G. Synthesis of *trans*-2,3-Cyclohexano-1,4,7,10,13-pentaazacyclopentadecane

trans-5,6-Cyclohexano-1,10,13-tris(*p*-toluenesulfonyl)-1,4,7,10,13-pentaazacyclopentadecan-3,8-dione prepar d as in Example 2D (1.765 g, 2.32 mmol) was suspended in 1,2-dimethoxy thane (dm , 40 ml) under argon, and the flask was placed in a water bath.

Lithium aluminum hydride (0.5 M in dme, 55 ml, 27.5 mmol) was added over a 5 min period. Five min later heating with a mantle was started, and reflux began 15 min later. The reaction became almost colorless after a few min of reflux, later turning yellow with white precipitate. Reflux was continued for 43.5 h, and then the reaction mixture was allowed to cool to room temperature. The reaction was quenched by the careful addition of water (0.86 ml) using a water bath for cooling. Five min later, 15% aqueous sodium hydroxide solution (0.86 ml) was added followed by water (2.6 ml). The slight yellowish color largely discharged during this process. One h later, tetrahydrofuran (55 ml) was added and stirring was continued for 2 h. The quenched reaction mixture was filtered. The filtrate was evaporated under reduced pressure and placed on the vacuum line, giving a yellowish-white solid. This solid was dissolved in dichloromethane and filtered, then concentrated to a solid and placed on the vacuum line. It was recrystallized from hot acetonitrile under argon, producing 0.316 g (50% yield) of white needles : mp 112-3 ° C (under nitrogen); ^1H NMR ($CDCl_3$) δ 0.97 (m, 2 H), 1.22 (m, 2H), 1.39 - 1.96 (3 m, 7 H), 2.11 (m, 4 H), 2.49 (m, 2 H), 2.54 - 2.88 (several m, 12 H), 2.94 (m, 2 H); Exact mass $(M + H)^+$: calcd, 270.2658; found, 270.2658 ($C_{14}H_{32}N_5$).

<u>H. Synthesis of [Manganese(II)dichloro(*trans*-2,3-Cyclohexano-1,4,7,10,13-pentaazacyclopentadecane)]</u>

trans-2,3-Cyclohexano-1,4,7,10,13-pentaazacyclopentadecane prepared as in Example 2G (301 mg, 1.12 mmol) was added to a hot anhydrous MeOH solution (50 ml) containing anhydrous manganese(II) chloride (140 mg, 1.12 mmol) under a dry nitrogen atmosphere. After refluxing for 2 h, the s lution was stirred vernight at room temperature and was then taken to dryness. The white solid was dissolved in warm

acetone (15 ml) and the solution was filtered. The solution was stripped to dryness and the white solid was washed with ethyl ether. The solid was dried in vacuo to give 0.36 g (82% yield) of product: FAB mass spectrum (NBA) m/z (relative intensity) 394 (M^+, 1), 359/361 [$(M-Cl)^+$, 100/29]; Anal. calcd. for $C_{14}H_{31}N_5MnCl_2$: C, 42.54; H, 7.91; N, 17.72. Found: C, 42.56; H, 8.17; N, 17.42.

Example 3

A. Synthesis of Boc-DAla-Ala-OEt

To a solution of Boc-DAla (25.0 g, 132.1 mmol) in DMF (1450 ml) was added HOBT•H_2O (19.8 g, 129.3 mmol) and EDC•HCl (28.0 g, 146.3 mmol) and the resulting solution was allowed to stir at RT for 30 min. To this solution was added Alanine ethyl ester hydrochloride (20.3 g, 132.1 mmol) and TEA (20.4 ml, 146.3 mmol) and the reaction was allowed to stir for 3 days (for convenience). The DMF was evaporated and the residue was partitioned between water (500 ml) and ethyl acetate (500 ml). The ethyl acetate solution was washed with 1N $NaHSO_4$ (250 ml), water (250 ml), saturated $NaHCO_3$ (250 ml), brine (250 ml) and dried over Na_2SO_4. Filtration and concentration afforded 31.7 g (83 % yield) of the desired dipeptide as a white foam: ^1H NMR (DMSO-d_6) δ 1.14 (d, J = 7.4 Hz, 3 H), 1.16 (t, J = 7.4 Hz, 3 H), 1.24 (d, J = 7.0 Hz, 3 H), 1.36 (s, 9 H), 3.96 - 4.09 (m, 3 H), 4.17 - 4.22 (apparent quintet, J = 7.4 Hz, 1 H), 6.77 (d, J = 7.7 Hz, 1 H), 8.09 (d, J = 7.0 Hz, 1 H); MS (LRCI, CH_4) m/z (relative intensity) = 317 (5) $[M + C_2H_5]^+$, 289 (60) $[M + H]^+$.

B. Synthesis of Boc-Ala-Ala-OH

T a suspension of the dipeptid (15.0 g, 93.6 mmol) in THF (192 ml) was added 0.5 N NaOH solution (192 ml). To

the resulting soluti n was added di-t-butyldicarbonate (26.6 g, 121.7 mmol) at once. The pH of the reaction was maintained at ~10 for 5 h and the mixture was then allowed to stir overnite. The pH of the reaction was again adjusted to ~10 and the solution was extracted with ethyl acetate (2 x 100 ml). The pH of the aqueous layer was adjusted to ~3.5 with aqueous potassium bisulfate and this mixture was extracted with ethyl acetate (3 x 100 ml). The combined extracts were dried ($MgSO_4$), filtered and concentrated to afford 20.7 g (85 % yield) of the desired product as a white powder: ^1H NMR (DMSO-d_6) δ 1.16 (d, J = 6.8 Hz, 3 H), 1.28 (d, J = 7.3 Hz, 3 H), 1.38 (s, 9 H), 3.95 - 4.09 (m, 1 H), 4.20 (quintet, J = 7.3 Hz, 1 H), 6.87 (d, J = 8.0 Hz, 1 H), 8.00 (d, 7.3 Hz, 1 H); MS (HRFAB, NBA - Li) m/z = 267.1557 [M + Li]+; 267.1532 calcd for $C_{11}H_{20}N_2O_5Li$.

C. Synthesis of DAla-Ala-OEt•TFA

The protected dipeptide (31.4 g, 109 mmol) was dissolved in methylene chloride (200 ml) and TFA (66 ml) was added. The resulting solution was allowed to stir for 30 min at RT and concentrated. The residue was coevaporated with methylene chloride (2 x 200 ml), dissoved in ether and oiled out with the addition of excess hexanes. The solvents were decanted and the residue was pumped at high vacuum for 12 h to afford 39.6 g (100 % yield, contains residual TFA) of the desired TFA salt as an orange oil: ^1H NMR (DMSO-d_6) δ 1.16 (t, J = 7.0 Hz, 3 H), 1.28 (d, J = 7.0 Hz, 3 H), 1.34 (d, J = 7.0 Hz, 3 H), 3.86 (bs, 1H), 4.07 (q, J = 7.0 Hz, 2 H), 4.26 (quintet, J = 7.0 Hz, 1 H), 8.21 (bs, 3 H), 8.86 (d, J = 7.4 Hz, 1 H); MS (LRCI, CH_4) m/z (relative intensity) 217 (5) $[M + C_2H_5]^+$, 189 (40) $[M+H]^+$.

D. Synthesis of Boc-Ala-Ala-DAla-Ala-OEt

To a solution of Boc-Ala-Ala-OH (20.1 g, 77.2 mmol) in DMF (850 ml) was added HOBT•H_2O (13.1 g, 85.4 mmol) and EDC•HCl (16.4 g, 85.4 mmol). To this solution was added DAla-Ala-OEt•TFA (23.3 g, 77.2 mmol) followed by TEA (11.9 ml, 85.4 mmol) and the resulting mixture was stirred for 12 h thereafter. The DMF was evaporated and the residue was dissolved in ethyl acetate (300 ml) and washed with 1 N potassium bisulfate (150 ml), water (150 ml), saturated sodium bicarbonate (150 ml) and brine (150 ml). The ethyl acetate layer was dried ($MgSO_4$), filtered and concentrated to half volume and crystallization was allowed to proceed. Isolation by filtration afforded 20.5 g (62 % yield) of the desired tetrapeptide as a white solid: ^1H NMR (DMSO-d_6) δ 1.13 (d, J = 7.0 Hz, 3 H), 1.17 (two coincidental d, J = 7.0 Hz, 6 H), 1.25 (d, J = 7.4 Hz, 3 H), 3.91 - 4.30 (m, 6 H), 6.87 (d , 7.0 Hz, 1 H), 7.92 (d, J = 6.3 Hz, 1 H), 8.07 (d, J = 7.3 Hz, 1 H), 8.09 (d, J = 6.6 Hz, 1 H); MS (HRFAB, NBA - Li) m/z = 437.2600 $[M + Li]^+$; 437.2588 calcd for $C_{19}H_{34}N_4O_7Li$.

E. Synthesis of Boc-Ala-Ala-DAla-Ala-OH

A solution of Boc-Ala-Ala-DAla-Ala-OEt (10.9 g, 25.3 mmol) in methanol (100 ml) was treated with 2.5 M sodium hydroxide (20.0 ml, 50.0 mmol) and the resulting solution was allowed to stir for 2 h at RT. At this time the pH of the solution was lowered to ~3 with the addition of aqueous potassium bisulfate and the resulting mixture was extracted with ethyl acetate (3 x 100 ml). The combined extracts were dried ($MgSO_4$), filtered and concentrated to afford 6.8 g (67 % yield of the desired acid as a white solid: ^1H NMR (DMSO-d_6) δ 1.17 (d, J = 7.2 Hz, 3 H), 1.20 (two coincidental d, J = 7.1 Hz, 6 H), 1.28 (d, J = 1.3 Hz, 3 H), 1.38 (s, 9 H), 3.90 - 4.00 (m, 1 H), 4.17 - 4.30 (m, 3 H), 6.93 (d, J =

6.7 Hz, 1 H), 7.96 (d, J = 6.7 Hz, 1 H), 8.04 (d, J = 7.4 Hz, 1 H), 8.07 (d, J = 7.8 Hz, 1 H); MS (HRFAB, NBA - Li) m/z = 409.2331 $[M + Li]^+$; 409.2353 calcd for $C_{17}H_{30}N_4O_7Li$.

F. Synthesis of Boc-Ala-Ala-DAla-Ala-DAla-OBzl

To a solution of Boc-Ala-Ala-DAla-Ala-OH (6.5 g, 16.3 mmol) in DMF (180 ml) was added HOBT•H_2O (2.86 g, 18.7 mmol) and EDC•HCl (3.58 g, 18.7 mmol). The resulting solution was allowed to stir for 15 min at RT and treated with DAla-OBzl p-toluenesulfonate salt (6.57 g, 18.7 mmol) and TEA (2.6 ml, 18.7 mmol). This mixture was allowed to stir for 12 h thereafter. The DMF was evaporated and the residue was partitioned between ethyl acetate (300 ml) and water (300 ml). The ethyl acetate layer was washed with 1 N potassium bisulfate (150 ml), water (150 ml), saturated sodium bicarbonate (150 ml) and brine (150 ml). The ethyl acetate layer was then dried ($MgSO_4$), filtered and concentrated to afford 9.0 g (100 % yield) of the desired compound as a white powder: ^1H NMR (DMSO-d_6) δ 1.17 (d, J = 7.3 Hz, 3 H), 1.21 (two conincidental d, J = 7.0 Hz, 6 H), 1.22 (d, J = 7.0 Hz, 3 H), 1.32 (d, J = 7.3 Hz, 3 H), 1.37 (s, 9 H), 3.90 - 4.09 (m, 1 H), 4.18 - 4.34 (m, 4 H), 5.13 (ABq, J = 12.7, Δ^v = 10.5 Hz, 2 H), 6.94 (d, J = 7.3 Hz, 1 H), 7.30 - 7.41 (m, 5 H), 7.97 (d, J = 7.0 Hz, 1 H), 8.10 - 8.18 (m, 2 H), 8.25 (d, J = 6.9 Hz, 1 H); MS (HRFAB, NBA - Li) m/z = 570.3140 $[M + Li]^+$; 570.3115 calcd for $C_{27}H_{41}N_5O_8Li$.

G. Synthesis of Ala-Ala-DAla-Ala-DAla•HCl

Boc-Ala-Ala-DAla-Ala-DAla-OEt (10.4 g, 18.7 mmol) was dissolv d in acetic acid (225 ml) and tr ated with concentrated hydrochloric acid (75 ml). The r sultin solution was allowed to stir at RT for 14 h thereafter. At this time the reaction was c ncentrated, coevaporated

with water (50 ml) and azeotropically dried by toluene coevaportation (2 x 100 ml) to afford 7.8 g (96 % yield) of the deprotected pentapeptide hydrochloride as a white powder: ^{1}H NMR (D_2O) δ 1.29 - 1.39 (m, 12H), 1.47 (d, J = 7.0 Hz, 3 H), 4.06 (q, J = 7.0 Hz, 1 H), 4.18 - 1.38 (m, 4 H); MS (LRFAB, NBA - HCl) 374 $[M + H]^+$.

H. Synthesis of *Cyclo*-(Ala-Ala-DAla-Ala-DAla-)

To a solution of Ala-Ala-DAla-Ala-DAla•HCl (7.8 g, 19.0 mmol) in DMF (2400 ml) at -40 °C was added DPPA (6.29 g, 22.8 mmol) and enough TEA to adjust the "pH" to ~8 (measured by spotting the reaction mixture on moistened hydrion paper). This solution was allowed to stand at -23 °C for 48 hours and at 8 °C for 48 hours. During this time the "pH" was again maintained at ~8 with the periodic addition of TEA. At the end of this period the reaction mixture was poured into water (2400 ml) and stirred with mixed-bed ion exchange resin (1200 g) for 6 h. The resin was removed by filtration and the filtrate was concentratedto a volume of ~ 100 ml. Ether (500 ml) was added and the precipitated white solid was isolated by filtration and washed with more ether (250 ml). The solid was then triturated by stirring with THF (100 ml) for 12 h (to remove traces of DMF), filtered and thoroughly dried to afford 3.15 g (47 % yield) of the desired cyclic peptide as a fine white powder: ^{1}H NMR (DMSO-d_6) δ 1.08 - 1.25 (m, 12 H), 1.24 (d, J = 7.3 Hz, 3 H), 4.00 - 4.10 (m, 1 H), 4.26 - 4.30 (m, 2 H), 4.34 (q, J = 7.2 Hz, 1 H), 4.41 (q, J = 7.6 Hz, 1 H), 7.58 (d, J = 7.0 Hz, 1 H), 7.83 (d, J = 8.4 Hz, 1 H), 8.22 (d, J = 6.2 Hz, 1 H), 8.33 (d, J = 7.81, 1 H), 8.49 (d, J = 6.8 Hz, 1 H); MS (HRFAB, NBA - HCl) m/z 356.1989 $(M + H)^+$; 356.1934 calcd for $C_{15}H_{25}N_5O_5$ $(M + H)^+$.

I. Synthesis of (2S, 5R, 8S, 11R, 14S)-Pentamethyl-1,4,7,10,13-pentaazacyclopentadecane

To a stirred suspension of *cyclo*-(Ala-Ala-DAla-Ala-DAla-) (3.10 g, 8.70 mmol) in THF (70 ml) at RT was added lithium aluminum hydride (108 ml of a 1.0 M solution in THF, 108 mmol). The resulting mixture was stirred at RT for 2 h and heated to reflux for 16 h thereafter. The mixture was then cooled to --20 °C and quenched with the dropwise addition of saturated sodium sulfate (~30 ml). The resulting mixture was concentrated to a dry white powder and this powder was triturated with ether (2 x 150 ml). The combined triturates were concentrated and recrystallized form acetonitrile to afford 1.10 g (44 % yield) of the desired ligand as a white solid: ^1H NMR ($CDCl_3$) δ 0.96 (d, J = 5.2 Hz, 3 H), 1.00 (two coincidental d, J = 5.0 Hz, 6 H), 1.02 (two coincidental d, J = 5.0 Hz, 6 H), 1.30 - 1.55 (bm, 2 H), 1.85 - 2.15 (bs, 3 H), 2.05 - 2.19 (m, 5 H), 2.42 - 3.00 (complex m, 12 H); MS (HRFAB, NBA - HCl) m/z = 286.3013 (M + H)$^+$; 286.2971 calcd for $C_{15}H_{36}N_5$.

J. Synthesis of [Manganese(II)dichloro-(2S, 5R, 8S, 11R, 14S)-Pentamethyl-1,4,7,10,13-pentaazacyclopentadecane

To a stirred solution of anhydrous $MnCl_2$ (79.0 mg, 0.62 mmol) in hot ethanol (5 ml) was added (2S, 5R, 8S, 11R, 14S)-pentaazacyclopentadecane (177 mg, 0.62 mmol). The solution was refluxed for 1 h and stirred at RT for an additional 16 h. The solution was filtered through celite, concentrated to half volume and treated with ether (30 ml). The white crystals were isolated by filtration and dried in vacuo to afford 187 mg (73 % yield) of the complex as a white solid: MS (LRFAB, NBA) m/z (relativ intensity) = 410 (5) [M]$^+$, 375/377 (100/30) [M - Cl]$^+$; Anal. calcd. for $C_{15}H_{35}N_5MnCl_2$: C,

43.75; H, 8.57; N, 17.01. Found: C,43.74; H, 8.60; N, 16.97.

Example 4

A. Synthesis of N-(p-toluenesulfonyl)-(R,R)-1,2-diaminocyclohexane

To a stirred solution of (R,R)-1,2-diaminocyclohexane (300 g, 2.63 mole) in CH_2Cl_2 (5.00 l) at -10° C was added a solution of p-toluenesulfonylchloride (209 g, 1.10 mole) in CH_2Cl_2 (5.00 l) dropwise ofer a 7 h period, maintaining the temp at -5 to -10° C. The mixture was allowed to warm to room temp while stirring overnight. The mixture was concentrated in vacuo to a volume of 3 l and the white solid was removed by filtration. The solution was then washed with H_2O (10 x 1 l) and was dried over $MgSO_4$. Removal of the solvent in vacuo gave 286 g (97.5 % yield) of the product as a yellow crystalline solid: ^1H NMR ($CDCl_3$) δ 0.98 - 1.27 (m, 4 H), 1.54 - 1.66 (m, 2 H), 1.81 - 1.93 (m, 2 H), 2.34 (dt, J = 4.0, 10.7 Hz, 1 H), 2.42 (s, 3 H), 2.62 (dt, J = 4.2, 9.9 Hz, 1 H), 7.29 (d, J = 8.1 Hz, 2 H), 7.77 (d, J = 8.3 Hz, 2 H); MS (LRFAB - DTT - DTE) m/z 269 $[M + H]^+$.

B. Synthesis of N-(p-toluenesulfonyl)-N'-(Boc)-(R,R)-1,2-diaminocyclohexane

To a stirred solution of N-(p-toluenesulfonyl)-(R,R)-1,2-diaminocyclohexane prepared as in Example 1A (256 g, 0.955 mole) in THF (1.15 l) was added a 1 N solution of aqueous NaOH (1.15 l, 1.15 mole). Di-t-butyldicarbonate (229 g, 1.05 mole) was then added and the resulting mixture was stirred overnight. The layers were separated and the aqueous layer was adjusted to pH 2 with 1 N HCl and saturated with NaCl. The aqueous soluti n was then extracted with CH_2Cl_2 (2 x 500 ml) and the extracts and THF layer wer combined and dried over

$MgSO_4$. The solvent was removed in vacuo to give a yellow solid. The crude product was purified by crystallization from a THF-ether-hexanes mixture to give 310 g (88.1% yield) of the product as a white crystalline solid: mp: 137 - 139° C; ^1H NMR ($CDCl_3$) δ 1.04 - 1.28 (m, 4 H), 1.44 (s, 9 H), 1.61 - 1.69 (m, 2 H), 1.94 - 2.01 (m, 2 H), 2.43 (s, 3 H), 2.86 (brs, 1 H), 3.30 (br d, J = 9.6 Hz, 1 H), 4.37 (br d, J = 6.7 Hz, 1 H), 5.48 (br d, J = 4.6 Hz, 1 H), 7.27 (d, J = 9.7 Hz, 2 H), 7.73 (d, J = 8.1 Hz, 2 H); MS (LRFAB, NBA - Li) m/z 375 $[M + Li]^+$.

C. Synthesis of Boc-(R,R)-Cyc(Ts)-gly-OMe

To a stirred solution of N-(p-toluenesulfonyl)-N'-(Boc)-(R,R)-1,2-diaminocyclohexane prepared as in Example 1B (310 g, 0.841 mole) in anhydrous DMF (3.11 l) at 0° C was added NaH (37.4 g - 60 % in oil, 0.934 mole) in portions and the resulting mixture was stirred for 30 min. Methyl bromoacetate (142 g, 0.925 mole) was then added dropwise over 45 min and the mixture was allowed to warm to room temp while stirring overnight. After stirring for 17 h, the solvent was removed in vacuo and the residue was dissolved in ethyl acetate(3 l) and H_2O (1 l). The ethyl acetate solution was washed with saturated $NaHCO_3$ (1 l), saturated NaCl (500 ml) and was dried over $MgSO_4$. The solvent was removed in vacuo and the resulting oil was dissolved in ether. Crystallization by the addition of hexanes gave 364 g (98 % yield) of the product (TLC (98:2 $CHCl_3$-MeOH/silica gel/UV detn) showed that the product contained about 5% starting material) as colorless needles: mp of pure sample 151 - 2° C ; ^1H NMR ($CDCl_3$) δ 1.11 - 1.22 (m, 4 H), 1.45 (s, 9 H), 1.64 - 1.70 (m, 3 H), 2.16 - 2.19 (m, 1 H), 2.43 (s, 3 H), 3.34 - 3.40 (m, 2 H), 3.68 (s, 3 H), 4.06 (ABq, J = 18.5 Hz, Δ υ = 155 Hz, 2H), 4.77 (br s 1 H), 7.30 (d, J = 8.3 Hz, 2 H),

7.82 (d; J = 8.3 Hz, 2 H); MS (LRFAB, DTT - DTE) m/z 441 $[M + H]^+$.

D. Synthesis of Boc-(R,R)-Cyc(Ts)-Gly-OH

To a stirred solution of impure Boc-(R,R)-Cyc(Ts)-Gly-OMe prepared as in Example 1C (217 g, 0.492 mole) in MeOH (1.05 l) was slowly added a 2.5N solution of aqueous NaOH (295 ml, 0.737 mole) and the resulting solution was stirred for 2 h. The solvent was removed in vacuo and the residue was dissolved in H_2O (1.5 l). The solution was filtered to remove a small amount of solid andwas washed with ether (7 x 1 l) to remove the impurity (compound 1B) which upon drying of the combined washes over $MgSO_4$ and removal of the solvent in vacuo resulted in recovery of 8.37 g. The pH of the aqueous solution was then adjusted to 2 with 1 N HCl and the product was extracted with ethyl acetate (3 x 1 l). The extracts were combined, washed with saturated NaCl (500 ml) and dried over $MgSO_4$. The solvent was removed in vacuo and the residual ethyl acetate removed by coevaporation with ether (500 ml) and then CH_2Cl_2 (500 ml) to give 205 g (97.6 % yield) of the product as a white foam : ^{1}H NMR ($CDCl_3$) δ 1.15 - 1.22 (m, 4 H), 1.48 (s, 9 H), 1.55 - 1.68 (m, 3 H), 2.12 - 2.15 (m, 1 H), 2.43 (s, 3 H), 3.41 - 3.49 (m, 2 H), 3.97 (ABq, J = 17.9 Hz, $\Delta\nu$ = 69.6 Hz, 2 H), 4.79 (br s, 1 H), 7.31 (d, J = 8.1 Hz, 2 H), 7.77 (d, J = 8.3 Hz, 2 H), 8.81 (br s, 1 H); MS (LRFAB, NBA - Li) m/z 433 $[M + Li]^+$.

E. Synthesis of N-(p-toluenesulfonyl)-(S,S)-1,2-diaminocyclohexane

To a stirred solution of (S,S)-1,2-diaminocyclohexan (300 g, 2.63 mole) in CH_2Cl_2 (5.00 l) at -10 °C was added a solution f p-toluenesulfonylchloride (209 g, 1.10 mole) in CH_2Cl_2 (5.00 l) dropwis over a 8 h peri d, maintaining the

temp at -5 to -10 °C. The mixture was allowed to warm to RT while stirring overnight. The mixture was concentrated in vacuo to a volume of 3 l and the white solid was removed by filtration. The solution was then washed with H_2O (10 x 1 l) and was dried over $MgSO_4$. Removal of the solvent in vacuo gave 289 g (98.3 % yield) of the product as a yellow crystalline solid: ^1H NMR ($CDCl_3$) δ 0.98 - 1.27 (m, 4 H), 1.55 - 1.66 (m, 2 H), 1.81 - 1.94 (m, 2 H), 2.32 (dt, J = 4.0, 10.9 Hz, 1 H), 2.42 (s, 3 H), 2.61 (dt, J = 4.0, 9.9 Hz, 1 H), 7.30 (d, J = 7.9 Hz, 2 H), 7.77 (d, J = 8.3 Hz, 2 H); MS (LRFAB,GT - HCl) m/z 269 $[M + H]^+$.

F. <u>Synthesis of N-(p-toluenesulfonyl)-N'-(Boc)-(S,S)-1,2-diaminocyclohexane</u>

To a stirred solution of N-(p-toluenesulfonyl)-(S,S)-1,2-diaminocyclohexane prepared as in Example 1E (289 g, 1.08 mole) in THF (1.29 l) was added a 1 N solution of aqueous NaOH (1.29 l, 1.29 mole). Di-t-butyldicarbonate (258 g, 1.18 mole) was then added and the resulting mixture was stirred overnight. The solid was removed by filtration and washed with THF. The THF layer was separated and the aqueous layer was adjusted to pH 2 with 1 N HCl and saturated with NaCl. The aqueous solution was then extracted with CH_2Cl_2 (2 x 500 ml) and the extracts and THF layer were combined, washed with saturated NaCl (500 ml) and dried over $MgSO_4$. The solvent was removed in vacuo to give a yellow slurry. Crystallization with the addition of ether gave 364 g (91.9 % yield) of the product as colorless needles: mp 137 - 139 °C; ^1H NMR ($CDCl_3$) δ 1.06 - 1.31 (m, 4 H), 1.44 (s, 9 H), 1.60 - 1.69 (m, 2 H), 1.95 - 1.99 (m, 2 H), 2.42 (s, 3 H), 2.86 (br s, 1 H), 3.30 (br d, J = 2.6 Hz, 1 H), 4.41 (br d, J = 7.3 Hz, 1 H), 5.54 (br d, J = 5.4

Hz, 1 H), 7.28 (d, J = 8.1 Hz, 2 H), 7.73 (d, J = 8.3 Hz, 2 H); MS (LRFAB, NBA - HCl) m/z 369 $[M + H]^+$.

G. Synthesis of Boc-(S,S)-Cyc(Ts)-gly-OMe

To a stirred solution of N-(p-toluenesulfonyl)-N'-(Boc)-(S,S)-1,2-diaminocyclohexane prepared as in Example 1F (364 g, 0.989 mole) in anhydrous DMF (3.66 l) at 0° C was added NaH (47.4 g - 60 % in oil, 1.19 mole) in portions and the resulting mixture was stirred for 1.5 h. The mixture was warmed to room temp and stirred an additional 30 min and then cooled back to 0° C. Methyl bromoacetate (189 g, 1.24 mole) was added dropwise over 30 min and the mixture was allowed to warm to RT while stirring overnight. After stirring for 17 h, the solvent was removed in vacuo and the residue was dissolved in a mixture of ethyl acetate(3 l) and H_2O (1 l). The layers were separated and the ethyl acetate solution was washed with saturated $NaHCO_3$ (1 l), H_2O (1 l), saturated NaCl (2 x 500 ml) and was dried over $MgSO_4$. The solvent was removed in vacuo and the resulting oil was dissolved in ether. Crystallization by the addition of hexanes gave 290 g of the crude product as yellow needles. Another 180 g was recovered from the filtrate as an oil. TLC (98:2 $CHCl_3$-MeOH/silica gel/UV detn) showed that both the solid and the oil contained starting material. ^1H NMR ($CDCl_3$) δ 1.06 - 1.29 (m, 4 H), 1.44 (s, 9 H), 1.58 - 1.66 (m, 3 H), 2.17 - 2.19 (m, 1 H), 2.43 (s, 3 H), 3.28 - 3.43 (m, 2 H), 3.68 (s, 3 H), 4.25 (ABq, J = 18.5 Hz, $\Delta \upsilon$ = 115 Hz, 2H), 4.76 (br s 1 H), 7.31 (d, J = 8.3 Hz, 2 H), 7.83 (d, J = 8.3 Hz, 2 H); MS (LRFAB, NBA - Li) m/z 447 $[M + H]^+$.

H. Synthesis of Boc-(S,S)-Cyc(Ts)-Gly-OH

To a stirred solution of impur Boc-(S,S)-Cyc(Ts)-Gly-OMe prepared as in Example 1G (197 g, 0.447 mole) in

MeOH (925 ml) was slowly added a 2.5N solution of aqueous NaOH (268 ml, 0.670 mole) and the resulting solution was stirred for 2 h. The solvent was removed in vacuo and the residue was dissolved in H_2O (1 l). The solution was washed with ether (4 x 1 l) to remove the impurity (compound 1F) which upon drying of the combined washes over $MgSO_4$ and removal of the solvent in vacuo resulted in recovery of 14.8 g. The pH of the aqueous solution was then adjusted to 2 with 1 N HCl and the product was extracted with ethyl acetate (3 x 1 l). The extracts were combined, washed with saturated NaCl and dried over $MgSO_4$. The solvent was removed in vacuo to give 171 g (89.7 % yield) of the product as an oil which crystallized on standing: ^1H NMR ($CDCl_3$) δ 1.10 - 1.22 (m, 4 H), 1.45 (s, 9 H), 1.55 - 1.68 (m, 3 H), 2.13 - 2.16 (m, 1 H), 2.43 (s, 3 H), 3.39 - 3.41 (m, 2 H), 4.00 (ABq, J = 18.1 Hz, $\Delta\upsilon$ = 80.4 Hz, 2 H), 4.82 (br s, 1 H), 7.31 (d, J = 8.3 Hz, 2 H), 7.75 (d, J = 8.3 Hz, 2 H), 9.28 (br s, 1 H); MS (LRFAB, NBA - Li) m/z 433 $[M + Li]^+$.

I. Synthesis of Boc-(S,S)-Cyc(Ts)-Gly-Gly-OEt

To a stirred solution of Boc-(S,S)-Cyc(Ts)-Gly-OH prepared as in Example 1H (26.7 g, 62.5 mmole) in degassed anhydrous DMF (690 ml) was added HOBT (10.1 g, 75.0 mmole) and EDC-HCl (14.4 g, 75.0 mmole). After the resulting solution was stirred for 30 min, glycine ethyl ester hydrochloride (9.60 g, 68.8 mmole) was added and the pH adjusted to 8 with TEA. After stirring for 2.75 days the solvent was removed in vacuo. The residue was dissolved in a mixture of ethyl acetate (1 l) and H_2O (1 l) and the layers were separated. The aqueous layer was extracted with ethyl acetate (1 l) and the extracts were combin . The ethyl acetate solution was washed with 0.1 N HCl (1 l), saturated $NaHCO_3$ (1 l), saturat d NaCl (500 ml) and was dried over $MgSO_4$. The solvent was removed

in vacuo to give 30.2 g (94.4 % yield) of the product as a white foam: ^1H NMR ($CDCl_3$) δ 1.19 - 1.23 (m, 3 H), 1.28 (t, J =7.05 Hz, 3 H), 1.42 (s, 11 H), 1.63 - 1.71 (m, 2 H), 2.16 - 2.18 (m, 1 H), 2.43 (s, 3 H), 3.50 - 3.57 (m, 2 H), 3.83 (ABq, J = 17.7 Hz, delta v = 35.7 Hz, 2 H), 4.01 (dABq, J = 6.05, 17.92 Hz, $\Delta \upsilon$ = 28.9 Hz, 2 H), 4.20 (q, J = 7.3 Hz, 2 H), 4.88 (br s, 1 H), 7.31 (d, J = 8.3 Hz, 2 H), 7.36 (br s, 1 H), 7.73 (d, J = 8.3 Hz, 2 H); MS (LRFAB, NBA - HCl) m/z 512 $[M + H]^+$.

J. Synthesis of (S,S)-Cyc(Ts)-Gly-Gly-OEt TFA salt

To a stirred solution of Boc-(S,S)-Cyc(Ts)-Gly-Gly-OEt prepared as in Example 1I (30.1 g, 58.8 mmole) in CH_2Cl_2 (265 ml) was added TFA (63 ml) and the resulting solution was stirred for 30 minutes. The solvent was removed in vacuo and residual TFA was coevaporated with CH_2Cl_2 (2 x 1 l) and ether (1 l). The oil was then triturated with ether (2 x 1 l) and the ether decanted. The resulting foam was dried in vacuo to give 33.7 g (assumed quantitative yield) of the product as a tan powder: ^1H NMR ($CDCl_3$) δ 0.96 - 1.23 (m, 4 H), 1.25 (t, J = 7.3 Hz, 3 H), 1.51 - 1.66 (m, 3 H), 2.12 - 2.26 (m, 1 H), 2.41 (s, 3 H), 2.98 - 3.10 (brs, 1 H), 3.67 - 3.71 (m, 1 H), 4.04 (ABq, J = 17.7 Hz, $\Delta \upsilon$ = 154 Hz, 2 H), 4.04 (d, J = 4.4 HZ, 2 H), 4.17 (q, J = 7.3 Hz, 2 H), 7.29 (d, J = 8.3 Hz, 2 H), 7.70 (d, J = 8.3 Hz, 2 H), 8.04 (br s, 1 H), 8.14 (br s, 3 H) MS (LRFAB, NBA - HCl) m/z 412 $[M + H]^+$.

K. Synthesis of Boc-(R,R)-Cyc(Ts)-Gly-(S,S)-Cyc(Ts)-Gly-Gly-OEt

To a stirred solution of Boc-(R,R)-Cyc(Ts)-Gly-OH prepared as in Example 1D (25.1 g, 58.8 mmole) in degassed anhydrous DMF (650 ml) was added HOBT (9.54 g, 70.6 mmole) and EDC-HCl (13.5 g, 70.6 mmole). After the resulting solution was stirred f r 30 min (S,S)-Cyc(Ts)-

Gly-Gly-OEt TFA salt prepared as in Example 1J (33.6 g, 58.8 mmole) was added and the pH was adjusted to 8 with TEA. After stirring for 2.75 days, the solvent was removed in vacuo. The residue was dissolved in a mixture of ethyl acetate (1 l) and H_2O (1 l) and the layers were separated. The ethyl acetate solution was washed with 0.1 N HCl (2 x 1 l), saturated $NaHCO_3$ (2 x 1 l), saturated NaCl (500 ml) and was dried over $MgSO_4$. The solvent was removed in vacuo to give 47.5 g (98.4 % yield) of the product as a tan foam: ^1H NMR ($CDCl_3$) δ 1.12 - 1.83 (m, 26 H), 2.21 - 2.24 (m, 2 H), 2.42 (s, 3 H), 2.43 (s, 3 H), 3.36 - 3.51 (br s, 2 H), 3.68 -3.96 (m, 6 H), 4.00 (d, J = 5.4 Hz, 2 H), 4.19 (q, J = 7.1 Hz, 2 H), 4.72 (br s, 1 H), 6.78 (br s, 1 H), 7.31 (d, J = 8.1 Hz, 4 H), 7.46 (br s, 1 H), 7.79 (m, 4 H); MS (LRFAB, NBA - HCl) m/z 820 $[M + H]^+$.

L. Synthesis of Boc-(R,R)-Cyc(Ts)-Gly-(S,S)-Cyc(Ts)-Gly-Gly-OH

To a stirred solution of Boc-(R,R)-Cyc(Ts)-Gly-(S,S)-Cyc(Ts)-Gly-Gly-OEt prepared as in Example 1K (47.4 g, 57.8 mmole) in MeOH (240 ml) was added a 2.5 N solution of aqueous NaOH (34.7 ml, 86.7 mmole) and the resulting solution was stirred for 2 h. The solvent was removed in vacuo and the residue was dissolved in H_2O (1 l). The aqueous solution was washed with ether (2 x 1 l) and the pH was adjusted to 2 with 1 N HCl. The solution was then saturated with NaCl and extracted with ethyl acetate (3 x 1 l). The combined extracts were dried over $MgSO_4$ and the solvent was removed in vacuo. The residual ethyl acetate was removed by coevaporation with CH_2Cl_2 and the resulting foam was dried in vacuo to give 45.7 g (99.7 % yield) f the product as a tan powd r: ^1H NMR ($CDCl_3$) δ 1.16 - 1.75 (m, 23 H), 2.13 - 2.17 (m, 2 H), 2.41 (s, 3 H), 2.42 (s, 3 H), 3.49 - 4.16 (m, 10 H), 4.53 (br s, 1 H), 7.01 (br s, 1 H), 7.30 (d,

J = 8.1 Hz, 4 H), 7.40 (br s, 1 H), 7.79 (d, J = 8.1 Hz, 2 H), 7.86 (d, J = 7.7 Hz, 2 H), 10.40 (br s, 1 H); MS (LRFAB, NBA - HCl) m/z 792 $[M + H]^+$.

M. Synthesis of (R,R)-Cyc(Ts)-Gly-(S,S)-Cyc(Ts)-Gly-Gly-OH TFA salt

To a stirred solution of Boc-(R,R)-Cyc(Ts)-Gly-(S,S)-Cyc(Ts)-Gly-Gly-OH prepared as in Example 1L (45.5 g, 57.5 mmole) in CH_2Cl_2 (260 ml) was added TFA (60 ml). The resulting solution was stirred for 30 min and the solvent was removed in vacuo. Residual TFA was removed by coevaporation with CH_2Cl_2 (3 x 1 l) and trituration of the resulting foam with ether (1 l, 2 x 750 ml), decanting the ether each time. After dessication in vacuo, 47.4 g (100 % yield) of the product was was obtained as an off white powder: ^1H NMR ($CDCl_3$) δ 1.05 - 1.31 (m, 9 H), 1.48 - 1.63 (m, 5H), 2.11 - 2.21 (m, 2 H), 2.40 (s, 3 H), 2.42 (s, 3 H), 3.25 (br s, 1 H), 3.60 - 3.80 (m, 3 H), 3.83 - 4.19 (m, 6 H), 6.94 (br s, 1 H), 7.31 (m, 4 H), 7.69 (m, 4 H), 7.83 (br s, 3 H), 13.17 (br s, 2 H); MS (LRFAB, DTT - DTE) m/z 692 $[M + H]^+$.

N. Synthesis of Cyclo-[(R,R)-Cyc(Ts)-Gly-(S,S)-Cyc(Ts)-Gly-Gly-]

To a stirred solution of (R,R)-Cyc(Ts)-Gly-(S,S)-Cyc(Ts)-Gly-Gly-OH TFA salt prepared as in Example 1M (32.2 g, 40.0 mmole) in degassed anhydrous DMF (10.0 l) at -78° C was added DPPA (13 4 g, 48.8 mmole). The pH of the solution was then adjusted to 8 with TEA and the solution was allowed to stand for 6 h at -78° C. The pH was readjusted to 8 with TEA and the solution was warmed to -45 ° C for 24 h. After readjusting the pH as before, the solution was allowed to warm to -40° C f r 24 h. The pH was adjusted as bef r and the solution was allow d to stand at -20° C f r 24 h. Th pH was readjust d as before and the soluti n was all wed t

warm to 2° C over 24 h. The pH had dropped only slightly. The pH was readjusted as before and the solution was allowed to stand at 2° C for another 24 h after which time the pH had not changed. The solution was divided equally among 6 - 4 l beakers and H_2O (1.1 l) was addedto each. Then added a total of 5.00 kg mixed-bed ion exchange resin to the solution (divided equally among the 6 beakers) and stirred the mixtures for 6 h. The resin was then filtered and washed with DMF. The solvent was then removed in vacuo and the solid residue was dissolved in MeOH (100 ml) and filtered to remove finely divided solids. The solution was then concentrated in vacuo to a volume of 25 ml and ether was added periodically as the crystallization proceeded to give 22.2 g (82.5 % yield) of the product as colorless needles; mp 190 - 200° C; ^1H NMR ($CDCl_3$) δ 0.87 - 2.13 (m, 16 H), 2.41 (s, 3 H), 2.45 (s, 3 H), 3.56 - 3.97 (m, 10 H), 6.66 (br s, 1 H), 7.18 (br s, 1 H), 7.34 (d, J = 8.1 Hz, 4 H), 7.65 (br s, 1 H), 7.71 (d, J = 7.3 Hz, 2 H), 7.39 (d, J = 7.3 Hz, 2 H); MS (LRFAB, NBA - Li) m/z 680 $[M + Li]^+$.

O. Synthesis of 2,3-(R,R)-8,9-(S,S)-Bis-cyclohexano-1,4,7,10,13-pentaazacyclopentadecane

To a stirred solution of Cyclo-[(R,R)-Cyc(Ts)-Gly-(S,S)-Cyc(Ts)-Gly-Gly] prepared as in Example 1N (19.4 g, 28.8 mmole) in anhydrous THF (475 ml) was added a solution of 1.0 M $LiAlH_4$ in THF (345 ml, 345 mmole) dropwise over 30 min. The yellow homogeneous solution was refluxed for 20 h (by which time it had become heterogeneous) and was then cooled to 0° C. The mixture was then quenched by the dropwise addition of a 10 % $NaSO_4$ solution (50 ml) while cooling in an ice bath. The solids were removed by filtration under an Ar blanket and the THF was removed in vacuo t give an oil which rapidly crystallized. The solids were then refluxed

with anhydrous THF (1 l) for 1 h and the mixture was filtered and the solvent removed in vacuo as before. The solids were then refluxed with a mixture of THF (1 l) and MeOH (500 ml) for 1 h and worked up as before. The residues from the extractions were then dissolved in anhydrous THF, combined and solids were removed by filtration. The solvent was removed in vacuo and the yellow foam dried by azeotroping H_2O with toluene (1.75 l) in vacuo at 90° C. Then refluxed the solids with hexanes (1 l) for 30 min and transferred the hot solution to a tared flask and removed the solvent in vacuo to give 6.1 g of an oil which crystallized on standing. The remaining solids were refluxed with hexanes as before and obtained 1.4 g of an oil which crystallized on standing. The solids were then dissolved in MeOH and toluene (1 l) was added. The solvent was removed in vacuo and any remaining H_2O was removed by azeotroping with toluene (1 l) and then hexanes (3 x 1 l). The resulting fine powder was refluxed with hexanes (1 l) for 2 h under argon and filtered into a tared flask. The solvent was removed in vacuo to give 1.7 g oil which crystallized on standing. The crystalline residues from the 3 extracts were dissolved in hexanes and combined. A small amount of haziness was removed by filtration and the solution was concentrated to give 5.3 g (57 % yield) of product as a pale yellow crystalline solid. Recrystallization from acetonitrile gave 4.47 g (48.0 % yield) of a colorless crystalline solid: mp 107 - 8° C; ^1H NMR ($CDCl_3$) δ 0.95 - 1.01 (m, 4 H), 1.19 - 1.24 (m, 4 H), 1.70 - 1.73 (m, 4 H), 1.97 (br s, 5 H), 2.08 - 2.14 (m, 8 H), 2.49 - 2.68 (m, 6 H), 2.74 - 2.80 (m, 2 H), 2.85 - 2.90 (m, 2 H), 2.94 - 2.99 (m, 2 H); MS (LRFAB, NBA) m/z 324 $[M + H]^+$; Anal. calcd. for $C_{18}H_{37}N_5$: C, 66.83; H, 11.53; N, 21.65. Found: C, 66.80; H, 11.44; N, 21.71.

P. Synthesis of [Manganese(II) dichloro (2,3-(R,R)-8,9-(S,S)-Bis-cyclohexano-1,4,7,10,13-pentaazacyclopentadecane] chloride

To a stirred solution of anhydrous $MnCl_2$ (1.67 g, 13.3 mmole) in hot methanol (120 ml) was added 2,3-(R,R)-8,9-(S,S)-bis-cyclohexano-1,4,7,10,13-pentaazacyclopentadecane prepared as in Example 10 (4.30 g, 13.3 mmole) and the solution was refluxed and then stirred at room temp overnight. Crystallization from ether gave 5.11 g (85.6 % yield) of the product as an off-white crystalline solid: MS (LRFAB, NBA) m/z (relative intensity) 448 (2) $[M]^+$, 413/415 (100,33) $[M - Cl]^+$; Anal. calcd. for $C_{18}H_{37}N_5MnCl_2$: C, 48.11; H, 8.30; N, 15.59; Cl, 15.78. Found: C, 48.18; H, 8.32; N, 15.56; Cl, 15.75.

Example 5

A. Synthesis of Boc-DSer(OBzl)-OMe

To Boc-DSer(OBzl)-OH (15.0 g, 50.8 mmol) win ACN (250 ml) was added Cs2CO3 (33.0 g, 102 mmol) and methyl iodide (6.32 ml, 102 mmol) and the resulting mixture was stirred at RT for 3 h thereafter. At this time the reaction was filtered and concentrated. The residue was partitioned between water (250 ml) and ethyl acetate (250 ml). The ethyl acetate layer was dried (MgSO4), filtered and concentrated to afford 15.0 g (95 % yield) of the desired methyl ester as a white solid: ^1H NMR (DMSO-d_6) δ 1.40 (s, 9 H), 3.64 (s, 3 H), 3.58 - 3.73 (m, 2 H), 4.32 (bq, J = 6.2 Hz, 1 H), 4.49 (s, 2 H), 7.16 (bd, J = 6.2 Hz, 1 H), 7.25 - 7.38 (m, 5 H); MS (HRFAB, NBA - Li) m/z = 316.1768 $[M + Li]^+$; 316.1736 calcd for $C_{16}H_{23}O_5NLi$.

B. Synthesis of DSer(OBzl)-OMe•TFA

Boc-DSer(OBzl)-OMe (15.0 g, 48.6 mmol) was dissolved in methylene chloride (125 ml) and treated with TFA (32 ml). The resulting mixture was stirred at RT for 30 min and concentrated. The oil was triturated with ether (400 ml) to remove residual TFA to afford 15.9 g (>100 %yield, contains a small amount of residual TFA) of the desired TFA salt as a colorless oil: ^1H NMR (DMSO-d_6) δ 3.72 (s, 3 H), 3.73 - 3.83 (m, 2 H), 4.36 (bt, J = 3.3 Hz, 1 H), 5.50 (ABq, J = 12 Hz, $\Delta\nu$ = 24 Hz , 2 H), 7.27 - 7.37 (m, 5 H), 8.72 (bs, 3 H); MS (HRFAB, NBA - HCl) 210.1159 [M + H]$^+$; 210.1130 calcd for $C_{11}H_{16}NO_3$.

C. Synthesis of Boc-Ser(OBzl)-DSer(OBzl)-OMe

Boc-Ser(OBzl)-OH (14.5 g, 49.2 mmol) was dissolved in DMF (550 ml) and treated with HOBT•H_2O (9.03 g, 59.0 mmol) followed by EDC•HCl (11.3 g, 59.0 mmol). The resulting solution was stirred for 20 min at RT and treated with DSer(OBzl)-OMe•TFA (15.9 g, 49.2 mmol) and TEA (8.22 ml, 59 mmol) and this solution was allowed to stir for 12 h thereafter. The DMF was evaporated and the residue was taken up into ethyl acetate (300 ml). The ethyl acetate solution was washed with 1 N sodium bisulfate (100 ml), water (100 ml), saturated sodium bicarbonate (100 ml), brine (100 ml) and dried ($MgSO_4$). Filtration and concentration afforded 20.8 g (87 % yield) of the desired dipeptide as a white solid: ^1H NMR (DMSO-d_6) δ 1.37 (s, 9H), 3.57 - 3.75 (m, 4 H), 3.62 (s, 3 H), 4.35 - 4.50 (m, 1 H), 4.46 (s, 3 H), 4.57 - 4.63 (m, 1 H), 6.88 (d, J = 8.1 Hz, 1 H), 7.20 - 7.34 (m, 10 H), 8.34 (d, J = 8.1 Hz, 1 H); MS (HRFAB, NBA - Li) m/z = 493.2559 [M + Li]$^+$; 493.2526 calcd for $C_{26}H_{34}N_2O_7Li$.

D. Synthesis of Ser(OBzl)-DSer(OBzl)-OMe•TFA

Boc-Ser(OBzl)-D-Ser(OBzl)-OMe (20.4 g, 42.0 mmol) was dissolved int methylene chloride (170 ml) and TFA (43 ml) was added. The resulting mixture was stirred at RT for 30 min and concentrated. The residue was triturated with ether (400 ml) to remove excess TFA to afford 22.7 g (>100 %, contains excess TFA) of the desired TFA salt: ^1H NMR (DMSO-d_6) δ 3.59 - 3.64 (m, 1 H), 3.67 (s, 3 H), 3.70 - 3.85 (m, 3 H), 4.23 (bs, 1 H), 4.40 - 4.58 (m, 4 H), 4.60 - 4.70 (m, 1 H), 7.20 - 7.39 (m, 10 H), 8.41 (bs, 3 H), 9.09 (d, J = 7.81 Hz, 1 H); MS (HRFAB, NBA - HCl) m/z = 387.1927 $[M + H]^+$; 387.1920 calcd for $C_{21}H_{27}N_2O_5$.

E. Synthesis of Boc-DSer(OBzl)-Ser(OBzl)-DSer(OBzl)-OMe

To a solution of Boc-DSer(OBzl)-OH in DMF (480 ml) was added HOBT•H_2O (7.96 g, 52.0 mmol) followed by EDC•HCl (9.97 g, 52.0 mmol) and the resulting solution was stirred for 20 min at RT. To this solution was added Ser(OBzl)-DSer(OBzl)-OMe•TFA (21.7 g, 43.3 mmol) and TEA (7.25 ml, 52.0 mmol) and the resulting mixture was stirred for 16 h thereafter. The DMF was evaporated and the residue was partitioned between water (100 ml) and ethyl acetate (300 ml). The ethyl acetate solution was washed with 1 N sodium bisulfate (150 ml), water (150 ml), saturated sodium bicarbonate (150 ml) and brine (150 ml), dried (Na_2SO_4), filtered and concentrated to afford 26.6 g (93 % yield) of the desired tripeptide as a white foam: ^1H NMR (DMSO-d_6) δ 1.39 (s, 9 H), 3.56 - 3.74 (complex m, 6 H), 3.64 (s, 3 H), 4.35 - 4.43 (m, 1 H), 4.43 -4.50 (m, 6 H), 4.63 (m, 1 H), 4.73 (m, 1 H), 6.94 (d, J = 7.8 Hz, 1 H), 7.24 - 7.36 (m, 15 H), 8.13 (d, J = 8.2 Hz, 1 H), 8.51 (d, J = 7.8 Hz, 1 H); MS (HRFAB, NBA - Li) m/z = 670.3326 $[M + Li]^+$; 670.3316 calcd for $C_{34}H_{45}N_3O_9Li$.

F. Synthesis of DSer(OBzl)-Ser(OBzl)-DSer(OBzl)-OMe•TFA salt

To a solution of Boc-DSer(OBzl)-Ser(OBzl)-DSer(OBzl)-OMe (26.4 g, 39.7 mmol) in methylene chloride (220 ml) was added TFA (55 ml) and the resulting solution was stirred at RT for 30 min and concentrated. The residue was triturated with ether (300 ml) and the ether triturate was decanted and dicarded affording 26.2 g (97 % yield) of the TFA salt as an orange oil after vacuum drying; ^{1}H NMR (DMSO-d_6) δ 3.55 - 3.3.83 (complex m, 6 H), 3.65 (s, 3 H), 4.21 (bs, 1 H), 4.40 - 4.58 (m, 6 H), 4.60 - 4.67 (m, 1 H), 4.85 -4.94 (m, 1 H), 7.20 - 7.40 (m, 15 H), 8.37 (bs, 3 H), 8.78 (d, J = 7.8 Hz, 1 H), 8.84 (d, J = 8.3 Hz, 1 H); MS (HRFAB, NBA - Li) m/z = 570.2790 [M + Li]$^+$; 570.2792 calcd for $C_{31}H_{37}N_3O_7Li$.

G. Synthesis of Boc-Ser(OBzl)-DSer(OBzl)-Ser(OBzl)-D-Ser(OBzl)-OMe

To a solution of Boc-Ser(OBzl)-OH (11.2 g, 38.0 mmol) was added HOBT•H2O (6.99 g, 45.6 mmol) and EDC•HCl (8.74 g, 45.6 mmol) and the resulting mixture was stirred at RT for 30 min. At this time DSer(OBzl)-Ser(OBzl)-DSer(OBzl)-OMe (25.8 g, 38.0 mmol) was added followed by TEA (6.36 ml, 45.6 mmol). The resulting solution was allowed to stir for 16 h thereafter. The DMF was evaporated and the residue was partitioned between water (200 ml) and ethyl acetate (400 ml). The ethyl acetate solution was washed with 1 N sodium bisulfate (200 ml), water (200 ml), saturated sodium bicarbonate (200 ml), and brine (200 ml), dried ($MgSO_4$), filtered and concentrated to afford 30.2 g (95 % yield) of the desired tetrapeptide as a white foam; ^{1}H NMR (DMSO-d_6) δ 1.38 (s, 9 H), 3.53 - 3.76 (complex m, 8 H), 3.64 (s, 3 H), 4.34 - 4.42 (m, 1 H), 4.40 - 4.51 (m, 8 H), 4.58 - 4.66 (m, 1 H), 4.67 - 4.77 (m, 1 H), 4.74 - 4.82 (apparent q, J = 7.8 Hz, 1 H), 6.89 (d, J = 8.2 Hz, 1

H), 7.22 - 7.38 (m, 20 H), 8.14 (d, J = 7.6 Hz, 1 H), 8.34 (d, J = 7.8 Hz, 1 H), 8.55 (d, J = 7.8 Hz, 1 H); MS (HRFAB, NBA - Li) m/z = 847.4095 [M + Li]$^+$; 847.4106 calcd for $C_{46}H_{56}N_4O_{11}Li$.

H. Synthesis of Ser(OBzl)-DSer(OBzl)-Ser(OBzl)-DSer(OBzl)-OMe•TFA

Boc-Ser(OBzl)-DSer(OBzl)-Ser(OBzl)-DSer(OBzl)-OMe (30.2 g, 35.9 mmol) was dissolved in methylene chloride (250 ml) and treated with TFA (63 ml). The resulting mixture was stirred for 30 min at RT and concentrated. Trituration with ether afforded 30.0 g (98 % yield) of the desired TFA salt as the oily residue; ^1H NMR (DMSO-d_6) δ 3.50 - 3.85 (complex m, 8 H), 3.65 (s, 3 H), 4.21 (bs, 1 H), 4.40 - 4.55 (m, 8 H), 4.58 - 4.66 (m, 1 H), 4.80 - 4.95 (m, 2 H), 7.20 - 7.40 (m, 20 H), 8.35 (bs, 3 H), 8.54 (d, J = 8.2 Hz, 1 H), 8.69 (d, J = 7.4 Hz, 1 H), 8.86 (d, J = 8.2 Hz, 1 H); MS (HRFAB, NBA - Li) m/z = 747.3590 [M + Li]$^+$; 747.3581 calcd for $C_{41}H_{48}N_4O_9Li$.

I. Synthesis of Boc-Ser(OBzl)-Ser(OBzl)-DSer(OBzl)-Ser(OBzl)-DSer(OBzl)-OMe

To a solution of Boc-Ser(OBzl)-OH (10.1 g, 34.2 mmol) in DMF (380 ml) was added HOBT•H_2O (6.28 g, 41.0 mmol) followed by EDC•HCl (7.86 g, 41.0 mmol) and the resulting mixture was stirred for 20 min at RT. Ser(OBzl)-DSer(OBzl)-Ser(OBzl)-DSer(OBzl)-OMe•TFA (29.2 g, 34.2 mmol) was added followed by the addition of TEA (5.71 ml, 41.0 mmol) and the reaction was allowed to stir for 12 h thereafter. The DMF was evaporated and the residue was partitioned between water (200 ml) and ethyl acetate (400 ml). The ethyl acetate layer was washed with 1 N sodium bisulfate (200 ml), water (200 ml), saturated sodium bicarbonat (200 ml) and brine (200 ml), dried ($MgSO_4$), filtered and concentrated to

afford 33.7 g (97 % yield) of the desired pentapeptide as a white powder; ^{1}H NMR (DMSO-d_6) δ 1.39 (s, 9 H), 3.55 - 3.77 (complex m, 10 H), 3.64 (s, 3 H), 4.32 - 4.42 (m, 1 H), 4.40 - 4.54 (m, 10 H), 4.60 - 4.68 (m, 1 H), 4.49 - 4.84 (m, 3 H), 7.00 (d, J = 7.7 Hz, 1 H), 7.20 - 7.40 (m, 25 H), 8.11 (d, J = 7.4 Hz, 1 H), 8.30 (d, J = 7.8 Hz, 1 H), 8.35 (d, J = 7.8 Hz, 1 H), 8.58 (d, J = 7.8 Hz, 1 H); MS (LRFAB, NBA - Li) m/z = 1024 [M + Li]$^+$.

<u>J. Synthesis Ser(OBzl)-Ser(OBzl)-DSer(OBzl)-Ser(OBzl)-DSer(OBzl)•HCl</u>

Boc-Ser(OBzl)-Ser(OBzl)-DSer(OBzl)-Ser(OBzl)-DSer(OBzl)-OMe (31.7 g, 31.1 mmol) was dissolved in acetic acid (760 ml) and treated with concentrated HCl (190 ml). The resulting solution was stirred at RT for 12 h thereafter. Concentration afforded 29.3 g (100 %) of the desired deprotected peptide salt as a white foam; ^{1}H NMR (DMSO-d_6) δ 3.55 - 3.90 (complex m, 10 H), 4.20 (m, 1 H), 4.38 - 4.61 (m, 11 H), 4.73 - 4.85 (m, 3 H), 7.20 - 7.40 (m, 25 H), 8.34 - 8.42 (m, 2 H), 8.49 (m, 4 H), 8.95 (d, J = 7.7 Hz, 1 H); (LRFAB, NBA - HCl] m/z = 905 [M + H]$^+$.

<u>K. Synthesis of *Cyclo*-[Ser(OBzl)-Ser(OBzl)-DSer(OBzl)-Ser(OBzl)-DSer(OBzl)-]</u>

A solution of Ser(OBzl)-Ser(OBzl)-DSer(OBzl)-Ser(OBzl)-DSer(OBzl)•HCl (29.4 g, 31.3 mmol) in anhydrous degassed DMF (4000 ml) was cooled to -40 °C and treated with DPPA (8.22 ml, 38.1 mmol) followed by TEA (4.53 ml, 32.5 mmol). The reaction was stored at -20 °C for 48 h and at 0 °C for 48 h thereafter. During this time the "pH" was maintained at ~8 by periodic addition of TEA (measured by spotting reaction mixtur on moistened Hydrion pap r). After this reaction period the reacti n was diluted with water (1000 ml) and stirred with mixed

bed i n-exchange resin (1600 g) for 6 h. The resin was removed by filtration and the filtrate was concentrated to a volume of ~200 ml. The product was precipitated by the addition of water (500 ml). The solid was filtered and washed with ether (250 ml) to afford after vacuum desiccation 20.5 g (74 % yield) of the desired cyclic peptide as a white powder: ^1H NMR ($DMSO-d_6$, *major conformer*) δ 3.50 - 3.83 (complex m, 11 H), 4.32 - 4.82 (complex m, 14 H), 7.18 - 7.38 (m, 25 H), 7.56 (d, J = 6.8 Hz, 1 H), 7.94 (d, J = 8.7 Hz, 1 H), 8.50 (d, J = 6.0 Hz, 1 H), 8.78 (m, 2 H); ; (LRFAB, NBA - Li] m/z = 893 $[M + Li]^+$.

L. Synthesis of (2S, 5R, 8S, 11R, 14S)-Penta(benzyloxymethyl)-1,4, 7, 10, 13-pentaazacyclopentadecane.

To a solution of the *Cyclo*-[Ser(OBzl)-Ser(OBzl)-DSer(OBzl)-Ser(OBzl)-DSer(OBzl)-] (7.00 g, 7.90 mmol) in THF (100 ml) was added lithium aluminum hydride (100 ml of a 1.0 M solution in THF, 100 mmol) over 5 min at RT. The resulting solution was heated at reflux for 16 h thereafter. The mixture was cooled to --20 °C and quenched (cautiously) with 5% sodium sulfate solution (30 ml). The resulting mixture was concetrated to a white powder and this powder was thoroughly dried by coevaporation with toluene (3 x 50 ml). The residue was triturated with ether (2 x 100 ml) and the combined triturates were concentrated to afford 6.1 g (95 % yield) of the desired ligand as a yellow oil; ^1H NMR ($CDCl_3$) δ 1.95 (bs, 5 H), 2.30 - 3.60 (complex m, 25 H), 4.20 - 4.40 (m, 10 H), 7.00 - 7.38 (m, 25 H); MS (HRFAB, NBA - Li) m/z = 822.5174 $[M + Li]^+$; 822.5146 calcd for $C_{50}H_{65}N_5O_5Li$.

M. Synthesis of [Manganese(II)dichloro(2S, 5R, 8S, 11R, 14S)-penta(hydroxymethyl)-1,4,7, 10,13-pentaazacyclopentadecane.

To a solution fo manganese(II) chloride (221 mg, 1.76 mmol) in methanol (75 ml) was added (2S, 5R, 8S, 11R, 14S)-penta(benzyloxymethyl)-1,4,7,10,13-pentaazacyclopentadecane (1.43 g, 1.75 mmol) and the reaction mixture was refluxed for 2 h and stirred at RT for 12 h thereafter. The methanol solution was evaporated and the residual oil was redissolved in ethanol (10 ml) and water (1 ml) in a Parr bottle. This mixture was treated with 10 % Pd on carbon (1 g) and hydrogenolyzed at 60 °C and 65 psi for 16 h thereafter. Filtration, concentration and recyrstallization from ethanol-ether afforded 212 mg (29 % yield) of the desired complex as a white solid; MS (HRFAB, NBA) m/z = 455.1718 $[M - Cl]^+$; 455.1707 calcd for $C_{15}H_{35}N_5MnCl$.

Example 6

Relaxivity measurements of the complexes of the invention (Examples 2-5) and of a comparative complex (Example 1) were determined and the results are found in Table I.

Proton relaxation times (T_1) of the sample in 100mM Hepes buffer, pH=7.4, at 40°C were determined from a monoexponential curve fit obtained from inversion-recovery pulse sequences (180°-τ-90°) with a Bruker PC 120/125/10 VTs NMR process analyzer. The spectrometer was calibrated for each sample to assure accurate duration of 90° and 180° radio frequency pulses and appropriate magnetic field strength to match the 20 MHz system operating frequency. The relaxivity (R_1) was obtained from the slope of a plot of $1/T_1$ versus the concentration of paramagnetic compound.

The relaxation time (T_2) of each sample in 100 mM Hepes buffer, pH=7.4, was measured at 40°C using a Carr-Purcel-Meiboom-Gill pulse sequence on the same Bruker instrument. The relaxivity (R_2) was obtained from a plot of $1/T_2$ versus the concentration of the paramagnetic compound.

Table I

Sample	Relaxivity, $mM^{-1}sec^{-1}$	
	R_1	R_2
Example 1 (Comparative)	1.82	2.37
Example 2	2.09	2.49
Example 3	2.76	3.86
Example 4	2.10	2.61
Example 5	3.48	5.93

The results found in Table I demonstrate that the complexes of the invention (Examples 2-5) have improved relaxivities compared to the comparative complex (Example 1).

Example 7

Kinetic stability measurements of the complexes of the invention (Examples 2-4) and of the comparative complex (Example 1) were determined and the results are found in Table II.

The kinetic stability constant (k_{diss}) for each complex can be determined by observing the rate at which copper appears to replace manganese as the metal center of the manganese macrocyclic complexes at different pH's.

A Beckman model DU-70 UV/VIS spectrometer was set up to scan the wavelengths from 700 to 200 nanometers. Concentrations of the complexes were kept low enough to stay within the linear range of observable absorbents for the DU-70, which is below 2.00 absorbents units.

Since copper has an observable absorbency band within the experimental range of wavelengths and binding energies that are much higher than that of manganese, the replacement of copper for manganese as the metal center is almost instantaneous. Therefore, copper is a good choice as a tracer of the decomposition of manganese from the macrocyclic ligand system.

Table II

Example No.	Kinetic Stability, k_{diss} ($M^{-1}Sec^{-1}$)
1 (Comparative)	2814
2	1375
3	17.7
4	31.5
5	ND[1]

[1] Not Determined

The data in Table II demonstrates that the complexes of the invention (Examples 2-4) are substantially more kinetically stable than the comparative complex (Example 1).

Example 8

Oxidation potentials of the complexes of the invention (Examples 2-4) and of the comparative complex (Example 1) were determined and the results are found in Table III.

Cyclic voltammograms were run in methanol containing 0.18M tetrabutylammonium chloride under nitrogen using a glassy carbon electrode with a platinum reference electrode and ferrocene internal standard.

Table III

Example No.	Oxidation Potential, $E_{1/2}$ (volts)
1 (Comparative)	0.70
2	0.75
3	0.85
4	0.74
5	ND[1]

[1] Not Determined

The results in Table III demonstrates that the manganese(II) complexes of the invention (Examples 2-4) are more oxidatively stable than the comparative manganese(II) complex (Example 1).

Example 9

The partition coefficient (log P) of the complexes of the invention (Examples 2-5) and of a comparative complex of (Example 1) were determined and the results are found in Table IV.

The partition coefficient was determined by measuring the manganese contents in each of the buffer and octanol phases. About 5mg of sample was dissolved in a 5mL octanol saturated buffer solution (10 mM Hepes/150mM NaCl, pH=7.4). The sample solution was mixed with 5mL of buffer saturated octanol and shaken overnight. The mixed solution was centrifuged to separate the two phases. 2mL of solution (in duplicate) was taken from each phase and digested with an acid mixture. The prepared solutions were then measured for manganese using ICP-AES and/or ICP-MS. The log P value was calculated from the Mn(octanol)/Mn(buffer) ratio.

Table IV

Example No.	Partition Coefficient, log P
1 (Comparative)	-2.9
2	-1.9
3	-1.1
4	-0.76
5	-3.2

The r sults in Table IV demonstrat that the log P, i.e. lipophilicity or bi distribution, of the complexes

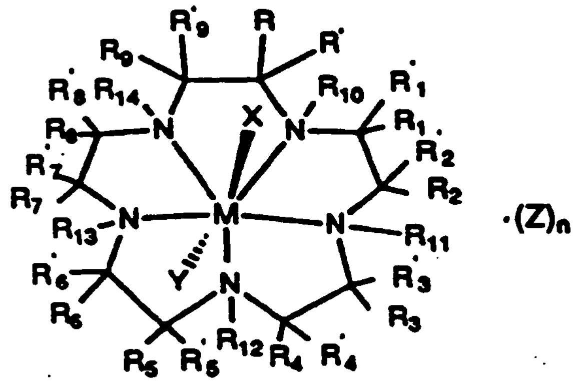
of the invention (Examples 2-5) can be controlled by controlling the substitutents on the macrocycle.

CLAIMS

That which is claimed is:

1. A method of magnetic resonance imaging comprising:

(a) administering to a human or non-human animal subject a contrast medium comprising a physiologically compatible complex represented by the formula:



wherein R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, and R', independently are selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylcycloalkyl, cycloalkenylalkyl, alkylcycloalkyl, alkenylcycloalkyl, alkylcycloalkenyl, alkenylcycloalkenyl, heterocyclic, aryl and aralkyl radicals and radicals attached to the α-carbon of α-amino acids; or R_1 or R'_1 and R_2 or R'_2, R_3 or R'_3 and R_4 or R'_4, R_5 or R'_5 and R_6 or R'_6, R_7 or R'_7 and R_8 or R'_8, and R_9 or R', and R or R' together with the carbon atoms to which they are attached independently form a saturated, partially saturated or unsaturated cyclic having 3 to 20 carbon atoms; R and R', R_1 and R'_1, R_2 and R'_2, R_3 and R'_3, R_4 and R'_4, R_5 and R'_5, R_6 and R'_6, R_7 and R'_7, R_8 and R'_8, and R_9 and R', together with the carbon atoms t which they are attached independently form a saturated, partially saturated, or

unsaturated ring structure having 3 to 20 carbon atoms; or one of R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, R'_9, R_{10}, R_{11}, R_{12}, R_{13} and R_{14} together with a different one of R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, R'_9, R_{10}, R_{11}, R_{12}, R_{13} and R_{14} which is attached to a different carbon or nitrogen atom in the macrocyclic ligand may be bound to form a strap represented by the formula

$$-(CH_2)_x-M-(CH_2)_w-L-(CH_2)_z-J-(CH_2)_y-$$

wherein w, x, y and z independently are integers from 0 to 10, and M, L and J are independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, alkaryl, alkheteroaryl, aza, amide, ammonium, thia, sulfonyl, sulfinyl, sulfonamide, phosphonyl, phosphinyl, phosphino, phosphonium, keto, ester, carbamate, urea, thiocarbonyl, borates, boranes, boraza, silyl, siloxy, silaza and combinations thereof; and R_{10}, R_{11}, R_{12}, R_{13} and R_{14} independently are selected from the group consisting of hydrogen, alkyl, and alkyl substituted with $-OR_{15}$, $-COOR_{15}$, $-CONR_{15}R_{16}$ or $-PO_3H_2$ wherein R_{15} and R_{16} are independently hydrogen or alkyl; wherein at least two of R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9 and R'_9 are other than hydrogen; wherein X, Y and Z are ligands independently selected from the group consisting of halide, oxo, aquo, hydroxo, alcohol, phenol, dioxygen, peroxo, hydroperoxo, alkylperoxo, arylperoxo, ammonia, alkylamino, arylamino, heterocycloalkyl amino, heterocycloaryl amino, amine oxides, hydrazine, alkyl hydrazine, aryl hydrazine, nitric oxide, cyanide, cyanate, thiocyanate, isocyanate, isothiocyanate, alkyl nitrile, aryl nitrile, alkyl isonitrile, aryl isonitrile, nitrat , nitrite, azido, alkyl sulfonic acid, aryl sulfonic acid, alkyl sulfoxid , aryl

sulfoxide, alkyl aryl sulfoxide, alkyl sulfenic acid, aryl sulfenic acid, alkyl sulfinic acid, aryl sulfinic acid, alkyl thiol carboxylic acid, aryl thiol carboxylic acid, alkyl thiol thiocarboxylic acid, aryl thiol thiocarboxylic acid, alkyl carboxylic acid, aryl carboxylic acid, urea, alkyl urea, aryl urea, alkyl aryl urea, thiourea, alkyl thiourea, aryl thiourea, alkyl aryl thiourea, sulfate, sulfite, bisulfate, bisulfite, thiosulfate, thiosulfite, hydrosulfite, alkyl phosphine, aryl phosphine, alkyl phosphine oxide, aryl phosphine oxide, alkyl aryl phosphine oxide, alkyl phosphine sulfide, aryl phosphine sulfide, alkyl aryl phosphine sulfide, alkyl phosphonic acid, aryl phosphonic acid, alkyl phosphinic acid, aryl phosphinic acid, alkyl phosphinous acid, aryl phosphinous acid, phosphate, thiophosphate, phosphite, pyrophosphite, triphosphate, hydrogen phosphate, dihydrogen phosphate, alkyl guanidino, aryl guanidino, alkyl aryl guanidino, alkyl carbamate, aryl carbamate, alkyl aryl carbamate, alkyl thiocarbamate, aryl thiocarbamate, alkylaryl thiocarbamate, alkyl dithiocarbamate, aryl dithiocarbamate, alkylaryl dithiocarbamate, bicarbonate, carbonate, perchlorate, chlorate, chlorite, hypochlorite, perbromate, bromate, bromite, hypobromite, tetrahalomanganate, tetrafluoroborate, hexafluoroantimonate, hypophosphite, iodate, periodate, metaborate, tetraaryl borate, tetra alkyl borate, tartrate, salicylate, succinate, citrate, ascorbate, saccharinate, amino acid, hydroxamic acid, thiotosylate, and anions of ion exchange resins, or the corresponding anions thereof, or X, Y and Z are independently attached to one or more of the "R" groups and n is an integer fr m 0 to 3;

M is a paramagnetic metal sel cted from th group consisting of metals having atomic numbers 21-29, 42-44

and 57-71; and a nontoxic, pharmaceutically acceptable carrier, adjuvant or vehicle; and

(b) generating a magnetic resonance image of at least a part of said subject.

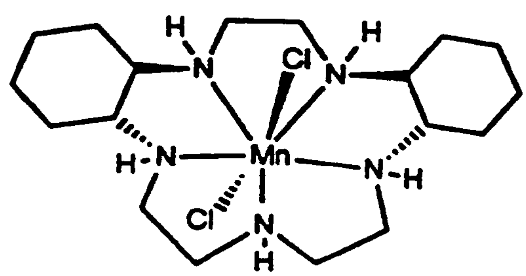
2. The method of Claim 1 wherein M is Mn(II) or Gd(III).

3. The method of Claim 2 wherein M is Mn(II).

4. The method of Claim 1 wherein at least three of R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9 and R'_9 are other than hydrogen.

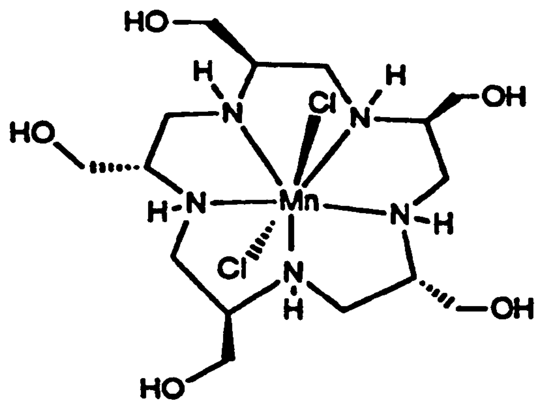
5. The method of Claim 1 wherein at least one of R_1 or R'_1 and R_2 or R'_2, R_3 or R'_3 and R_4 or R'_4, R_5 or R'_5 and R_6 or R'_6, R_7 or R'_7 and R_8 or R'_8, and R_9 or R'_9 and R or R' together with the carbon atoms to which they are attached form a saturated cyclic having 5 to 8 carbon atoms; and all of the remaining "R" groups are independently selected from hydrogen, alkyl, or alkyl substituted with $-OR_{15}$ or $-NR_{15}R_{16}$ wherein R_{15} and R_{16} are independently hydrogen or alkyl.

6. The method of Claim 5 wherein said complex is represented by the formula:



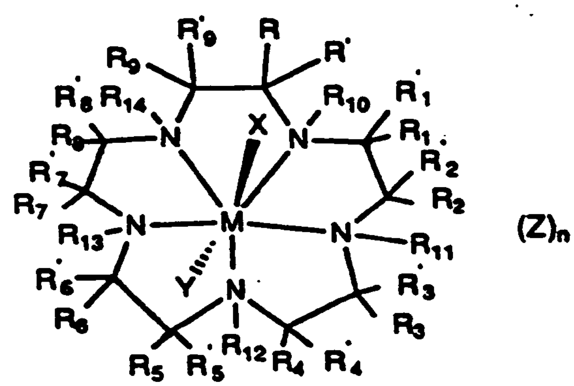
7. The method of Claim 1 wherein at least two of R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9 and R'_9 are alkyl or alkyl substituted with $-OR_{15}$ or $-NR_{15}R_{16}$ wherein R_{15} and R_{16} are independently hydrogen or alkyl.

8. Th m thod of Claim 7 wherein said complex is represent d by the f rmula:



9. A method of diagnostic imaging comprising:

(a) administering to a human or non-human animal subject a diagnostic agent comprising a physiologically compatible complex represented by the formula:



wherein R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, and R'_9 independently are selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylcycloalkyl, cycloalkenylalkyl, alkylcycloalkyl, alkenylcycloalkyl, alkylcycloalkenyl, alkenylcycloalkenyl, heterocyclic, aryl and aralkyl radicals and radicals attached t the α-carbon of α-amino acids; or R_1 or R'_1 and R_2 or R'_2, R_3 or R'_3 and R_4 r R'_4, R_5 or R'_5 and R_6 r R'_6, R_7 or R'_7 and R_8 or R'_8, and R_9 r R'_9 and R r R' together with the

carbon atoms to which they are attached independently form a saturated, partially saturated or unsaturated cyclic having 3 to 20 carbon atoms; R and R', R_1 and R'_1, R_2 and R'_2, R_3 and R'_3, R_4 and R'_4, R_5 and R'_5, R_6 and R'_6, R_7 and R'_7, R_8 and R'_8, and R_9 and R'_9 together with the carbon atoms to which they are attached independently form a saturated, partially saturated, or unsaturated ring structure having 3 to 20 carbon atoms; or one of R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, R'_9, R_{10}, R_{11}, R_{12}, R_{13} and R_{14} together with a different one of R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, R'_9, R_{10}, R_{11}, R_{12}, R_{13} and R_{14} which is attached to a different carbon or nitrogen atom in the macrocyclic ligand may be bound to form a strap represented by the formula

$$-(CH_2)_x- M -(CH_2)_w- L -(CH_2)_z- J -(CH_2)_y-$$

wherein w, x, y and z independently are integers from 0 to 10, and M, L and J are independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, alkaryl, alkheteroaryl, aza, amide, ammonium, thia, sulfonyl, sulfinyl, sulfonamide, phosphonyl, phosphinyl, phosphino, phosphonium, keto, ester, carbamate, urea, thiocarbonyl, borates, boranes, boraza, silyl, siloxy, silaza and combinations thereof; and R_{10}, R_{11}, R_{12}, R_{13} and R_{14} independently are selected from the group consisting of hydrogen, alkyl, and alkyl substituted with $-OR_{15}$, $-COOR_{15}$, $-CONR_{15}R_{16}$ or $-PO_3H_2$ wherein R_{15} and R_{16} are independently hydrogen or alkyl; wherein at least two of R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9 and R'_9 are other than hydrogen; wherein X, Y and Z are ligands independently selected from the group consisting of halid , oxo, aqu , hydroxo, alcohol, phenol, dioxygen, perox , hydroperoxo, alkylper x , arylperoxo, ammonia, alkylamino, arylamino, heterocycloalkyl amin ,

heterocycloaryl amino, amine oxides, hydrazine, alkyl hydrazine, aryl hydrazine, nitric oxide, cyanide, cyanate, thiocyanate, isocyanate, isothiocyanate, alkyl nitrile, aryl nitrile, alkyl isonitrile, aryl isonitrile, nitrate, nitrite, azido, alkyl sulfonic acid, aryl sulfonic acid, alkyl sulfoxide, aryl sulfoxide, alkyl aryl sulfoxide, alkyl sulfenic acid, aryl sulfenic acid, alkyl sulfinic acid, aryl sulfinic acid, alkyl thiol carboxylic acid, aryl thiol carboxylic acid, alkyl thiol thiocarboxylic acid, aryl thiol thiocarboxylic acid, alkyl carboxylic acid, aryl carboxylic acid, urea, alkyl urea, aryl urea, alkyl aryl urea, thiourea, alkyl thiourea, aryl thiourea, alkyl aryl thiourea, sulfate, sulfite, bisulfate, bisulfite, thiosulfate, thiosulfite, hydrosulfite, alkyl phosphine, aryl phosphine, alkyl phosphine oxide, aryl phosphine oxide, alkyl aryl phosphine oxide, alkyl phosphine sulfide, aryl phosphine sulfide, alkyl aryl phosphine sulfide, alkyl phosphonic acid, aryl phosphonic acid, alkyl phosphinic acid, aryl phosphinic acid, alkyl phosphinous acid, aryl phosphinous acid, phosphate, thiophosphate, phosphite, pyrophosphite, triphosphate, hydrogen phosphate, dihydrogen phosphate, alkyl guanidino, aryl guanidino, alkyl aryl guanidino, alkyl carbamate, aryl carbamate, alkyl aryl carbamate, alkyl thiocarbamate, aryl thiocarbamate, alkylaryl thiocarbamate, alkyl dithiocarbamate, aryl dithiocarbamate, alkylaryl dithiocarbamate, bicarbonate, carbonate, perchlorate, chlorate, chlorite, hypochlorite, perbromate, bromate, bromite, hypobromite, tetrahalomanganate, tetrafluoroborate, hexafluoroantimonate, hypophosphite, iodate, periodate, metaborate, t traaryl borate, t tra alkyl borate, tartrate, salicylate, succinate, citrate, ascorbate, saccharinate, amin acid, hydroxamic acid, thi tosylate, and anions of i n exchange resins, or the corresp nding

anions thereof, or X, Y and Z are independently attached to one or more of the "R" groups and n is an integer from 0 to 3;

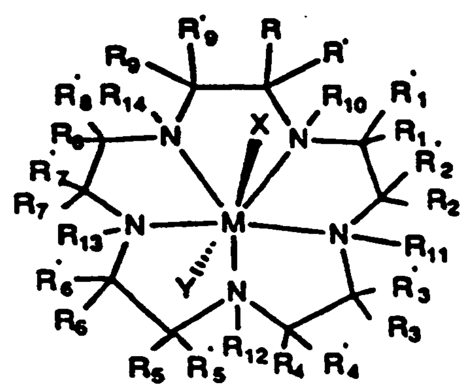
M is a heavy metal selected from the group consisting of metals having atomic numbers 20-32, 42-44, 49 and 57-83; and a nontoxic, pharmaceutically acceptable carrier, adjuvant or vehicle; and

(b) generating an X-ray, ultrasound or scintigraphic image of at least a part of said subject.

10. The method of Claim 9 wherein M is a radioactive metal isotope selected from the group consisting of ^{99m}Tc and ^{111}In and said image is a scintigraphic image.

11. The method of Claim 9 wherein at least three of R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9 and R'_9 are other than hydrogen.

12. A method of radiotherapy practiced on a human or non-human animal subject comprising administering to said subject a radioactive agent comprising a physiologically compatible complex represented by the formula:



$(Z)_n$

wherein R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, and R'_9 independ ntly are selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycl alk nyl, cycloalkylalkyl, cycloalkylcycloalkyl,

cycloalkenylalkyl, alkylcycloalkyl, alkenylcycloalkyl, alkylcycloalkenyl, alkenylcycloalkenyl, heterocyclic, aryl and aralkyl radicals and radicals attached to the α-carbon of α-amino acids; or R_1 or R'_1 and R_2 or R'_2, R_3 or R'_3 and R_4 or R'_4, R_5 or R'_5 and R_6 or R'_6, R_7 or R'_7 and R_8 or R'_8, and R_9 or R'_9 and R or R' together with the carbon atoms to which they are attached independently form a saturated, partially saturated or unsaturated cyclic having 3 to 20 carbon atoms; R and R', R_1 and R'_1, R_2 and R'_2, R_3 and R'_3, R_4 and R'_4, R_5 and R'_5, R_6 and R'_6, R_7 and R'_7, R_8 and R'_8, and R_9 and R'_9 together with the carbon atoms to which they are attached independently form a saturated, partially saturated, or unsaturated ring structure having 3 to 20 carbon atoms; or one of R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, R'_9, R_{10}, R_{11}, R_{12}, R_{13} and R_{14} together with a different one of R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, R'_9, R_{10}, R_{11}, R_{12}, R_{13} and R_{14} which is attached to a different carbon or nitrogen atom in the macrocyclic ligand may be bound to form a strap represented by the formula

$$-(CH_2)_x-M-(CH_2)_w-L-(CH_2)_z-J-(CH_2)_y-$$

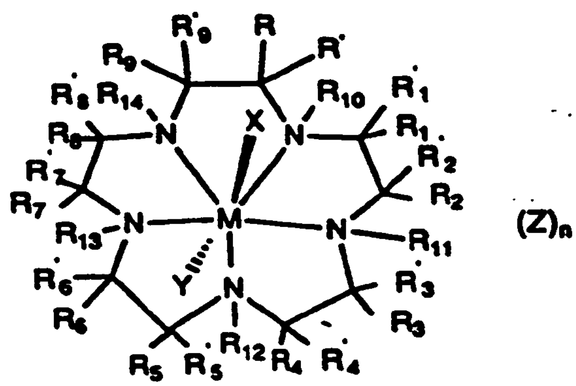
wherein w, x, y and z independently are integers from 0 to 10, and M, L and J are independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, alkaryl, alkheteroaryl, aza, amide, ammonium, thia, sulfonyl, sulfinyl, sulfonamide, phosphonyl, phosphinyl, phosphino, phosphonium, keto, ester, carbamate, urea, thiocarbonyl, borates, boranes, boraza, silyl, siloxy, silaza and combinations thereof; and R_{10}, R_{11}, R_{12}, R_{13} and R_{14} independently are selected from the group consisting of hydrogen, alkyl, and alkyl substituted with $-OR_{15}$, $-COOR_{15}$, $-CONR_{15}R_{16}$ r $-PO_3H_2$ wh rein R_{15} and R_{16} are independently hydrogen or alkyl; wherein at least tw of R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3,

R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9 and R'_9 are other than hydrogen; wherein X, Y and Z are ligands independently selected from the group consisting of halide, oxo, aquo, hydroxo, alcohol, phenol, dioxygen, peroxo, hydroperoxo, alkylperoxo, arylperoxo, ammonia, alkylamino, arylamino, heterocycloalkyl amino, heterocycloaryl amino, amine oxides, hydrazine, alkyl hydrazine, aryl hydrazine, nitric oxide, cyanide, cyanate, thiocyanate, isocyanate, isothiocyanate, alkyl nitrile, aryl nitrile, alkyl isonitrile, aryl isonitrile, nitrate, nitrite, azido, alkyl sulfonic acid, aryl sulfonic acid, alkyl sulfoxide, aryl sulfoxide, alkyl aryl sulfoxide, alkyl sulfenic acid, aryl sulfenic acid, alkyl sulfinic acid, aryl sulfinic acid, alkyl thiol carboxylic acid, aryl thiol carboxylic acid, alkyl thiol thiocarboxylic acid, aryl thiol thiocarboxylic acid, alkyl carboxylic acid, aryl carboxylic acid, urea, alkyl urea, aryl urea, alkyl aryl urea, thiourea, alkyl thiourea, aryl thiourea, alkyl aryl thiourea, sulfate, sulfite, bisulfate, bisulfite, thiosulfate, thiosulfite, hydrosulfite, alkyl phosphine, aryl phosphine, alkyl phosphine oxide, aryl phosphine oxide, alkyl aryl phosphine oxide, alkyl phosphine sulfide, aryl phosphine sulfide, alkyl aryl phosphine sulfide, alkyl phosphonic acid, aryl phosphonic acid, alkyl phosphinic acid, aryl phosphinic acid, alkyl phosphinous acid, aryl phosphinous acid, phosphate, thiophosphate, phosphite, pyrophosphite, triphosphate, hydrogen phosphate, dihydrogen phosphate, alkyl guanidino, aryl guanidino, alkyl aryl guanidino, alkyl carbamate, aryl carbamate, alkyl aryl carbamate, alkyl thiocarbamate, aryl thiocarbamate, alkylaryl thiocarbamate, alkyl dithiocarbamate, aryl dithiocarbamate, alkylaryl dithiocarbamate, bicarbonate, carbonate, perchl rate, chlorate, chlorite, hypochlorite, perbromate, bromate, bromite, hypobromite,

tetrahalomanganate, tetrafluoroborate, hexafluoroantimonate, hypophosphite, iodate, periodate, metaborate, tetraaryl borate, tetra alkyl borate, tartrate, salicylate, succinate, citrate, ascorbate, saccharinate, amino acid, hydroxamic acid, thiotosylate, and anions of ion exchange resins, or the corresponding anions thereof, or X, Y and Z are independently attached to one or more of the "R" groups and n is an integer from 0 to 3;

M is a radioactive metal selected from ^{153}Sm, ^{67}Cu or ^{90}Y; and a nontoxic, pharmaceutically acceptable carrier, adjuvant or vehicle.

13. A compound represented by the formula:



wherein R, R′, R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, and R'_9 independently are selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylcycloalkyl, cycloalkenylalkyl, alkylcycloalkyl, alkenylcycloalkyl, alkylcycloalkenyl, alkenylcycloalkenyl, heterocyclic, aryl and aralkyl radicals and radicals attached to the α-carbon of α-amino acids; or R_1 or R'_1 and R_2 or R'_2, R_3 or R'_3 and R_4 or R'_4, R_5 or R'_5 and R_6 or R'_6, R_7 or R'_7 and R_8 or R'_8, and R_9 or R'_9 and R or R′ together with the carbon atoms t which they are attached ind pendently form a saturated, partially saturated or unsaturated

cyclic having 3 to 20 carbon atoms; R and R', R_1 and R'_1, R_2 and R'_2, R_3 and R'_3, R_4 and R'_4, R_5 and R'_5, R_6 and R'_6, R_7 and R'_7, R_8 and R'_8, and R_9 and R'_9 together with the carbon atoms to which they are attached independently form a saturated, partially saturated, or unsaturated ring structure having 3 to 20 carbon atoms; or one of R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, R'_9, R_{10}, R_{11}, R_{12}, R_{13} and R_{14} together with a different one of R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, R'_9, R_{10}, R_{11}, R_{12}, R_{13} and R_{14} which is attached to a different carbon or nitrogen atom in the macrocyclic ligand may be bound to form a strap represented by the formula

$$\left(CH_2 \right)_x M \left(CH_2 \right)_w L \left(CH_2 \right)_z J \left(CH_2 \right)_y$$

wherein w, x, y and z independently are integers from 0 to 10, and M, L and J are independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, alkaryl, alkheteroaryl, aza, amide, ammonium, thia, sulfonyl, sulfinyl, sulfonamide, phosphonyl, phosphinyl, phosphino, phosphonium, keto, ester, carbamate, urea, thiocarbonyl, borates, boranes, boraza, silyl, siloxy, silaza and combinations thereof; and R_{10}, R_{11}, R_{12}, R_{13} and R_{14} independently are selected from the group consisting of hydrogen, alkyl, and alkyl substituted with $-OR_{15}$, $-COOR_{15}$, $-CONR_{15}R_{16}$ or $-PO_3H_2$ wherein R_{15} and R_{16} are independently hydrogen or alkyl; wherein at least two of R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9 and R'_9 are other than hydrogen;

wherein X, Y and Z are ligands independently selected from the group consisting of halide, oxo, aquo, hydroxo, alc h l, phenol, dioxygen, per x , hydroperox , alkylperoxo, arylperoxo, amm nia, alkylamino, arylamin , h terocycloalkyl amin , heterocycl aryl amin , amine

oxides, hydrazine, alkyl hydrazine, aryl hydrazine, nitric oxide, cyanide, cyanate, thiocyanate, isocyanate, isothiocyanate, alkyl nitrile, aryl nitrile, alkyl isonitrile, aryl isonitrile, nitrate, nitrite, azido, alkyl sulfonic acid, aryl sulfonic acid, alkyl sulfoxide, aryl sulfoxide, alkyl aryl sulfoxide, alkyl sulfenic acid, aryl sulfenic acid, alkyl sulfinic acid, aryl sulfinic acid, alkyl thiol carboxylic acid, aryl thiol carboxylic acid, alkyl thiol thiocarboxylic acid, aryl thiol thiocarboxylic acid, alkyl carboxylic acid, aryl carboxylic acid, urea, alkyl urea, aryl urea, alkyl aryl urea, thiourea, alkyl thiourea, aryl thiourea, alkyl aryl thiourea, sulfate, sulfite, bisulfate, bisulfite, thiosulfate, thiosulfite, hydrosulfite, alkyl phosphine, aryl phosphine, alkyl phosphine oxide, aryl phosphine oxide, alkyl aryl phosphine oxide, alkyl phosphine sulfide, aryl phosphine sulfide, alkyl aryl phosphine sulfide, alkyl phosphonic acid, aryl phosphonic acid, alkyl phosphinic acid, aryl phosphinic acid, alkyl phosphinous acid, aryl phosphinous acid, phosphate, thiophosphate, phosphite, pyrophosphite, triphosphate, hydrogen phosphate, dihydrogen phosphate, alkyl guanidino, aryl guanidino, alkyl aryl guanidino, alkyl carbamate, aryl carbamate, alkyl aryl carbamate, alkyl thiocarbamate, aryl thiocarbamate, alkylaryl thiocarbamate, alkyl dithiocarbamate, aryl dithiocarbamate, alkylaryl dithiocarbamate, bicarbonate, carbonate, perchlorate, chlorate, chlorite, hypochlorite, perbromate, bromate, bromite, hypobromite, tetrahalomanganate, tetrafluoroborate, hexafluoroantimonate, hypophosphite, iodate, periodate, metaborate, tetraaryl borate, tetra alkyl borate, tartrat , salicylat , succinate, citrate, ascorbate, saccharinate, amin acid, hydroxamic acid, thi tosylate, and anions of ion exchange resins, or the corresponding anions thereof, or X, Y and Z are ind pendently attached

to one or more of the "R" groups and n is an integer from 0 to 3;
M is a paramagnetic metal selected from the group consisting of metals having atomic numbers 21-29, 42-44 and 57-71; and
at least one of R_{10}, R_{11}, R_{12}, R_{13} and R_{14} is other than hydrogen.

14. The compound of Claim 13 wherein M is Mn(II) or Gd(III).

15. The compound of Claim 13 wherein at least three of R, R′, R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9 and R'_9 are other than hydrogen.

16. The compound of Claim 13 wherein at least one of R_1 or R'_1 and R_2 or R'_2, R_3 or R'_3 and R_4 or R'_4, R_5 or R'_5 and R_6 or R'_6, R_7 or R'_7 and R_8 or R'_8, and R_9 or R'_9 and R or R′ together with the carbon atoms to which they are attached form a saturated cyclic having 5 to 8 carbon atoms; and all of the remaining "R" groups are independently selected from hydrogen, alkyl, or alkyl substituted with $-OR_{15}$ or $-NR_{15}R_{16}$ wherein R_{15} and R_{16} are independently hydrogen or alkyl.

17. The compound of Claim 13 wherein at least two of R, R′, R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9 and R'_9 are alkyl or alkyl substituted with $-OR_{15}$ or $-NR_{15}R_{16}$ wherein R_{15} and R_{16} are independently hydrogen or alkyl.

INTERNATIONAL SEARCH REPORT

Inter. nal Application No
PCT/US 95/03763

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K49/00 A61K51/04 C07F13/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 296 522 (DOW CHEMICAL CO) 28 December 1988 see claims ---	9-12
X	EP,A,0 287 465 (GUERBET SA) 19 October 1988 see page 8, line 56 - page 9, line 21; claims ---	1-5,7, 13-17
X	DE,A,24 61 919 (DU PONT) 17 July 1975 see page 6; figure X; table I see page 1, paragraph 1 ---	13
X	WO,A,92 04919 (MALLINCKRODT MEDICAL INC) 2 April 1992 see claims --- -/--	1-5, 13-17

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 July 1995	01.08.95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	BERTE, M

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,92 21017 (UNGER EVAN C ;SHEN DEKANG (US)) 26 November 1992 see page 5; figure III see claims 42,50,77,86	1-5, 13-17
P,X	TETRAHEDRON LETT. (1994), 35(22), 3687-90 CODEN: TELEAY;ISSN: 0040-4039, ASTON, KARL W. ET AL 'Asymmetric synthesis of highly functionalized polyazamacrocycles via reduction of cyclic peptide precursors' see the whole document	13-17
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X	EP,A,0 524 161 (MONSANTO CO) 20 January 1993 see page 2, line 54 - page 4, line 15; claims	13-17
A	WO,A,82 04252 (BORREGAARD IND ;DALE JOHANNES (NO); BUOEN SOLFRID (NO); KRANE JOST) 9 December 1982	1-17
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INTERNATIONAL SEARCH REPORT

Inter. ...nal Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PATENT ABSTRACTS OF JAPAN vol. 12, no. 219 (C-506) 22 June 1988 & JP,A,63 014 780 (TOSOH CORP.) 21 January 1988 see abstract -----	1-17

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/03763

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark:Although claims 1-12 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-5,7,9-17
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
please see enclosure ../..!

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

Incomplete search,...
II. Obscurities, ...
In view of the definition of products by means of their biological, chemical and/or pharmacological properties, the search has to be restricted for economic reasons.
The search was limited to the compounds for which pharmacological data was given and/or the compounds mentioned in the claims or examples.
(See Guidelines, Part B, Chapt. III, paragraph 3.6)

INTERNATIONAL SEARCH REPORT

Interr ial Application No
PCT/US 95/03763

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INTERNATIONAL SEARCH REPORT

Interr al Application No
PCT/US 95/03763

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